Volume 23 • Issue 8 • December 2022

PEDIATRICDIABETES

ISPAD

International Society For Pediatric and Adolescent Diabetes

Clinical Practice Consensus Guidelines

December 2022

WILEY

Editor in Chief
Philip Zeitler, Denver, Colorado, USA

ISPAD
International Society for Pediatric and Adolescent Diabetes

Accepted: 2 November 2022
DOI: 10.1111/pedi.13449

REVIEWS AND COMMENTARIES

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

ISPAD Annual Conference 2022 highlights

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KEYWORDS: diabetes, ISPAD, Ispad highlights, pediatric

1 | PLENARY—ADVANCES IN DIABETES TREATMENT

Clinical trials performed in the last three decades have shown that restoration of beta-cell function via transplantation of isolated islet cells allowed the achievement of a more physiological release of endocrine hormones. The future of insulin-producing cells is expected to progress to implantation without requiring immunosuppression by using gene editing, allowing the production of immune-evasive cells. Viral infections have long been considered possible candidates for environmental triggers in genetically susceptible individuals with type 1 diabetes (T1D). Epidemiological studies have demonstrated that enterovirus infections are associated with the development of islet autoimmunity and T1D. The Diabetes Virus Detection (DiViD) study reported the presence of enterovirus genome by a polymerase chain reaction and of enterovirus proteins by immunohistochemistry in pancreatic sections. The evidence from the DiViD study could provide evidence that an enterovirus vaccine may potentially be effective for the primary and secondary prevention of T1D. A prospective, randomized controlled DiVid interventional study is now in progress, using antiviral treatment (pleconaril and ribavirin) for 6 months in newly diagnosed individuals with T1D. Novel immunotherapies for different T1D endotypes are currently underway, using bionics, chimeric antigen receptor (CAR)-engineered regulatory T cells (Tregs) and vaccination with tolerogenic dendritic cells. Currently, five immunotherapies have been shown to preserve insulin secretion in patients with newly diagnosed T1D: teplizumab, otelixizumab, rituximab, abatacept, low-dose anti-thymocyte globulin and alefacept, most of them having an acceptable safety profile and side effect. The expected approval

of teplizumab by the FDA and EMA will force the treatment paradigm of T1D to shift by placing a greater emphasis on screening for T1D and by driving the market revolving around individuals with T1D toward precision medicine.

2 | SYMPOSIUM—NUTRITION MANAGEMENT IN DIABETES

Continuous glucose monitoring (CGM) has become a routine part of clinical practice as it provides glucose metrics that healthcare professionals can analyze with families and provide valuable information regarding glucose control, moving from HbA1c outcomes to CGM metrics outcomes. Some of the key features to discuss with the families about CGM metrics include time in range, time above and below range and the visualization of the graphs allowing them to have a better comprehension of the impact of nutrition choices on glucose behavior. Families reported that CGM had increased their awareness of the different impacts of foods and snacks. The prevalence of celiac disease in T1D ranges from 1 to 16% worldwide. The greatest risk is associated with children diagnosed with T1D before 5 years of age and with longer diabetes duration. ISPAD and ADA recommend screening for celiac disease should be performed soon after diagnosis of T1D, and at 2 to 5 years intervals (sooner if symptomatic or having a first-degree relative with celiac disease). Literature indicates that the normalization time of celiac titers depends on the degree of serology elevation and severity of intestinal damage. In practice, it might take as long as 4 years, despite a strict gluten-free diet. Long-standing celiac disease in individuals with T1D increases the risk of retinopathy and nephropathy, higher bone fracture risk and higher rates of concomitant autoimmune thyroid disease. These individuals are at greater risk for depression and eating disorders.

3 | SYMPOSIUM—REGISTRIES: WHY ARE THEY IMPORTANT?

Registries are a systematic and organized way of data collection that helps in evaluating specific outcomes, as well as contributing to quality improvement, surveillance, and benchmarking. Registries play an important role in improving patients' care and serve as a reliable guide for health authorities, insurance companies and other health organizations. Collaborative comparisons between international pediatric diabetes registries and the blending of their data may pave the way for the development of more relevant international guidelines. There are multiple T1D registries globally. In 2016, the T1D Exchange Quality Improvement Collaborative (T1DX-QI) registry, included data from more than 50 centers in the United States of America. The Kuwaiti experience CODeR (Childhood Onset Diabetes Electronic Registry) was also developed in the Middle East. Registries are important tools and provide an important source of information that could help in monitoring the progression of the disease and the course of its complication, identify risk factors, estimate costs and direct resources, design prevention programs, and improve the standard of care locally and globally.

4 | PLENARY—DIGITALIZATION IN DIABETES EDUCATION AND CARE

The advances in diabetes technology have identified health inequalities within areas such as deprivation and ethnicity. Healthcare professionals are challenged to integrate technology and digitalization of diabetes education and care into routine diabetes management, but ensuring that underserved populations do not miss out is a key priority. "Big Data" collection helps to identify metabolic models for staging T1D and to identify therapeutic outcomes. It also allows healthcare professionals to identify individual outcomes and support those living with diabetes. "Voice bio marker identification" is being currently researched to identify vocal biomarkers for screening diabetes and monitoring the health of those living with the condition. The "Colive Voice Study" have recognized that those living with diabetes have distinct vocal signatures compared to the general population. The study aims to look at this research data being integrated into artificial intelligence delivery algorithms, using vocal assistance to support patient management and monitoring in the future.

5 | SYMPOSIUM—MENTAL HEALTH IN DIABETES

Diabetes burnout may be a result of the relentless daily tasks of living with T1D. Health professionals must recognize the difference between distress and depression. Depression is a psychiatric condition that is more than burnout or distress, and the symptoms interfere with day-to-day functions. Distress in teenagers is linked to worsening self-care behaviors and sub-optimal glycemic management. Diabetes distress is recognized to be higher within lower social economic groups and those with racial and ethnic minority backgrounds. However, teenagers with strong peer support have shown that they are less likely to experience diabetes distress. The statistics show that the prevalence of a clinically diagnosed eating disorder is greater in women with Type 1 diabetes and this is twice greater in adolescents with T1D. The physical and psychological impact of an eating disorder increases the risk of diabetic ketoacidosis, long-term complications associated with diabetes and strong negative emotions resulting in increased depression and suicidal thoughts. As health professionals, it is important to develop knowledge about eating disorders in those living with diabetes and to establish appropriate treatment pathways.

6 | SYMPOSIUM—UPDATES ON COVID AND DIABETES IN CHILDREN

During the COVID-19 pandemic, new approaches in clinical follow-up were developed using telemedicine consultations and remote educational sessions. Studies focusing on the doctor-patient relationship in synchronous real-time video consultations compared to in-person visits concluded that patient-care satisfaction and perception of the doctor-patient relationship, along with patients' perception of

physician empathy did not substantially differ between the two forms of consultation. Adults with T1D registered worsening of metabolic control associated with a significant reduction of physical activity during lockdown due to COVID-19 pandemic, which disagreed with data from pediatric participants. This difference may relate to the normal activity in children that can compensate for the lack of structured physical exercise. CoVidentary, an innovative online exercise training program created during the pandemic in Italy used social media to reduce sedentary behaviors in children with T1D during the pandemic and a virtual camp to monitor glycemic management. Exercise and nutrition advice and management were some of the initiatives developed to compensate lockdown restrictions and improve glycemic management.

7 | JOINT SYMPOSIUM—JDRF-ISPAD: ACCESS TO CARE CHALLENGES AND SOLUTIONS

The challenges of living with T1D are greater in low-middle-income countries (LMICs). These include limited health coverage for insulin, skilled multidisciplinary teams, and comprehensive diabetes education programs. Something unique to developing countries is that there is a large out-of-pocket expense that puts a disproportional burden for healthcare on those in low-income households. There are also issues related to the public health system which is overburdened and commonly provides varying standards of care in primary or tertiary settings, with a lack of regular follow-up or established registry to adequately track outcome data. Barriers to access to insulin in LMICs are related to regulation, production costs and complex regulatory assessment. Prescription issues include a lack of clinical guidelines, a lack of sustainable training for healthcare providers and a limited understanding of healthcare providers about biosimilars. Novel innovations in insulin and glucose testing need to meaningfully involve people with T1D and their caregivers from low-income settings Additional strategies to address challenges include removing barriers that hinder competition, ensuring that products on the market are quality assured by a regulatory authority, pooling procurement at the national level, ensuring price transparency in the supply chain and developing clinical guidelines within the health systems.

8 | SYMPOSIUM—PREDICTION AND PREVENTION OF TYPE 1 DIABETES

The vast majority of individuals that have two or more antibodies progress to T1D diagnosis. Progression differs by age, as those identified under the age of 9 progress faster, and those over the age of 20 progress more slowly. The concept of endotypes in T1D is based on the first autoantibody specificity and age at diagnosis (<7 years, 7–12 years, >12 years). Current investigations looking at the role of enterovirus in developing T1D found that IAA first endotype risk was associated with coxsackie B1, and no risk was seen with GADA. Primary prevention trials are currently investigating rituximab, teplizumab, abatacept, and autoantigen-specific therapy. Secondary prevention trials are investigating the use of anti-CD3, teplizumab, abatacept, hydroxychloroquine, golimumab, and liraglutide. Teplizumab treatment for 14 days was the first drug shown to be able to slow the disease process leading to T1D in high-risk individuals. Other developments have shown a rapid decline in gut microbiota diversity in those with T1D. Fecal transplantation can potentially improve diversity, rearrange gut metabolites with immunomodulatory effects, restore gut permeability, and incite changes in the immune system. In a study where individuals were randomized to receive stool from a healthy young donor or autologous feces from self, there was stabilization in fasting and stimulated c-peptide in both groups but not for all participants.

9 | PLENARY—OBESITY AND ITS MANAGEMENT

The prevalence of childhood obesity is increasing worldwide. Obesity in childhood is a multi-faceted disease with genetic, metabolic, environmental and behavioral factors that interact with each other. Greater severity of obesity is associated with a greater risk of low HDL cholesterol, high systolic and diastolic blood pressure, and high triglyceride and HbA1c. The ENDO Society recommends the use of drugs only after failure of lifestyle changes and pharmacotherapy options for children are limited. Orlistat reduces fat absorption by inhibiting pancreatic lipases but the safety/efficacy profile for children <12 years has not been established. Phentermine demonstrated enhanced weight loss in many, but there are several adverse events in adolescents, and it is currently only approved for >16 years. Liraglutide leads to a significantly greater reduction in BMI SD score with lifestyle changes compared to placebo, with greater improvements in BMI and body weight. Phentermine/topiramate offered statistically significant reductions in BMI and favorably impacted triglyceride and HDL-C levels in adolescents with obesity. The meta-analysis concluded that liraglutide had a higher probability of achieving clinically significant weight loss compared with other drugs, while topiramate was superior in safety. There are ongoing combination therapies being studied in adults and children that show combination therapy achieves higher weight loss, and patients prescribed >3 medications lost significantly more weight than those prescribed 2 or no anti-obesity medications at 12 months. Currently, the need to select therapy is based on affordability and insurance coverage. Bariatric surgery in adolescents have also demonstrated a higher likelihood of having remission of type 2 diabetes and hypertension compared to adults.

10 | SYMPOSIUM—UPDATES ON TECHNOLOGY IN DIABETES CARE

The iLet Bionic Pancreas could be the preferred option for patients with T1D in the future who want less interaction and a simpler

interface with the insulin delivery system as it requires no adjustments of basal rates and bolus settings, no carb counting or manual correction boluses, This investigational insulin delivery system is a closed loop system which uses a mono- (insulin) or bi- hormonal (insulin and glucagon) therapy. The glucose target is the only setting to adjust, and the device adapts continuously to the individual insulin needs and carbohydrate counting is not needed. In the pediatric cohort of 165 participants, HbA1c were 0.5% lower in patients with the bionic pancreas compared to those on standard care. Despite the increasing availability of licensed closed loops, open-source automated insulin delivery systems are still in the game. Arguments for open-source automated insulin delivery systems include technological advantages such as customizable personal profile, remote control of profile, unavailability of hybrid closed loop system in some countries, unachieved therapy goals and less frequent interaction with diabetes technology.

11 | JOINT SYMPOSIUM—ATTD-ISPAD: ADVANCED TECHNOLOGY IN DIABETES

Artificial intelligence is often used to describe machines that mimic human cognitive functions. Clinical Decision Support System (CDSS) provides clinicians, staff and individuals with knowledge and person-specific information to enhance their health care. A wide range of CDSS is available to cover all aspects of diabetes care and could be classified into the following groups: (1) tools for people with diabetes self-management (personalized nutrition support and physical activity), (2) screening and prevention for diabetes-related complications, (3) prediction tools for identification of people more likely to develop diabetes, and (4) clinical management support. The idea is to improve clinical outcomes, increase access to care, enhance the utilization of healthcare resources and provide precision medicine, allocating always the decision comparable to the one that an experienced physician would provide. Open-source automated insulin-delivery systems have been extensively studied, and are safe, effective and have the potential to help a wide population of individuals with T1D alongside commercial systems. Every healthcare professional is responsible to learn about all treatment options, including open-source systems while these systems should fully disclose how they operate to enable healthcare professionals and patients to understand the benefits and limits of these systems.

12 | JOINT SYMPOSIUM ASPED-ISPAD: DIABETES & FASTING

Fasting is a part of many religions, and the best example of this is Ramadan fasting. Advancing technology has made it possible to fast safely. The challenges of fasting with diabetes include the risk of hypoglycemia, hyperglycemia, ketoacidosis, dehydration and thrombosis. There are some exemptions from religious fasting such as very young age, women who are pregnant or breastfeeding, persons with intellectual disabilities and individuals who are travelling or doing heavy physical labor. If a person with T1D wishes to fast, a risk assessment is important. A New DaR-IDF Risk score is available to help in making this decision. Interventions should also be planned ahead to ensure safe fasting, and these include pre-fast counselling, pre-fast glycemic optimization, frequent blood glucose monitoring, insulin modifications, nutrition and activity. Blood glucose monitoring is an essential element to risk quantification for people wishing to fast. Pre-fasting nutritional education is crucial for safe fasting and an individualized dietary plan is needed to maintain a healthy body weight, avoid excessive weight changes and minimize complication risk. Necessary dietary modifications should be made such as type of food, time of meals, insulin regimen and ensuring knowledge about carbohydrate counting. Advancing technologies such as CGM have also made it possible to fast safely, as it provides an accurate and reliable understanding of blood glucose changes, duration of hyperglycemia as well as time in target.

13 | JOINT SYMPOSIUM ESPE-ISPAD: MONOGENIC AND OTHER FORMS OF DIABETES

Monogenic diabetes is a heterogenous condition, caused by one or more defects in a single gene or chromosomal locus. Combined, monogenic diabetes accounts for approximately 2.5%–6.5% of pediatric diabetes. The list of genes causing monogenic diabetes is growing fast (more than 50 genes have been identified so far, associated with either T-cell dysfunction (T1DB-like), insulin receptor defect (T2D-like), or monogenic autoimmunity) and this underscores the need for comprehensive next-generation sequencing (NGS) as the best diagnostic approach. Early and accurate diagnosis can guide treatment, rather than phenotype-based targeted testing, particularly for neonatal diabetes (NDM). Glibenclamide, which stimulates insulin release from pancreatic beta-cells by inhibiting ATP-sensitive potassium channels, could be used as a specific treatment of NDM due to KATP channel mutations. Glibenclamide is also a neuroprotective drug and has been shown to improve neurological features in NDM such as epilepsy, motor function, global neurological improvement, and hypotonia. Glibenclamide oral suspension (Amglidia) has been designed for premature, neonates, toddlers and children and is as efficient as tablets. Monogenic diabetes in Arab regions has a different spectrum and is mostly associated with a rare familial recessive syndrome. Neonatal diabetes is more common in Arabs and has a different genetic etiology compared to other populations, associated also with a higher rate of consanguinity. The most frequent etiology reported in this region is Wolcott-Rallison syndrome due to EIF2AK3 mutations. On the other hand, data on MODY in Arabs are limited, which might be due to unknown genetic mechanisms contributing to the pathogenesis of MODY in Arabs.

14 | SYMPOSIUM—IMPACT OF DIABETES ON BEHAVIOR

Sleep is vitally important in the early years of life, and it is fundamental for brain development. Humans spent a third of their lives asleep.

Out of six main categories of sleep disorders, diabetes mellitus contributes to two of them; "parasomnias" resulting from enuresis, and "sleep-related movement disorder," especially in people living with T1DM for a long time. Sleep disturbance could increase the vulnerability to some psychological disorders including depression. A chronic condition such as T1D that requires constant monitoring results in sleep disturbance due to several factors such as staying awake late to deal with hypoglycemia, waking during the night to correct for hyperglycemia, or struggling to fall asleep due to a late sweet snack. Sleep has to be kept high on the research agenda to learn how best to support families to find the balance between waking to manage diabetes and sleeping for health. Evidence-based intervention strategies include behavioral parent training in improving communication, encouraging behavior management, promoting structure within the family, and planning ahead. Digital interventions to improve self-care and mental health in young people such as the self-compassion chatbot "COMPASS" were found to be helpful in improving the well-being of adolescents living with T1DM. Future directions recommended include developing digital tools that incorporate evidence-based psychological theories, use of digital tools to augment face-to-face therapy, involving young people in the development and including parents and families in the delivery are needed.

15 | JOINT SYMPOSIUM ISPAE-ISPAD: DIABETES CARE SYSTEMS SET-UP

Task shifting and sharing involve the redistribution or delegation of healthcare tasks within the task workforce and communities. Task shifting occurs when a task is transferred or delegated while task sharing occurs when tasks are completed collaboratively between providers with different levels of training. The purpose of task sharing or shifting is to reduce morbidity, mortality and burden of the disease among the populations where a shortage or inaccessibility of highly skilled professional health workers limits access to effective care so that shifting or sharing achieves this purpose by positioning providers with less training to deliver effective interventions thereby improving access to and coverage of those interventions without compromising standards of care. In LMICs, patient access to multidisciplinary teams is limited. LFAC ISPAD-Task shifting survey reported on gaps in access to skilled medical, nursing and AHPs for young people with T1D in LMICs. The responsibility of T1D care in Uganda lies primarily at the primary healthcare centers and not at the tertiary hospitals. Care in Uganda is mainly provided by nurses working in isolated clinics with limited drugs and equipment. In Uganda, internet penetration is only about 26.2% of the total 47 million population, while only half the population has mobile phone connections. PEN-Plus is part of an ecosystem where care and treatment are provided at first-level district hospitals. Decentralizing of T1D care through the PEN-Plus was achieved by mid-level providers who are trained in T1D to facilitate follow-up and management of T1D.

16 | SYMPOSIUM—DIABETES PUBLICATIONS SPECIAL HIGHLIGHTS

Numerous studies were published in the last year describing clinical investigations of type 1 or type 2 diabetes care, including recent findings in the understanding of diabetes etiology and possible prevention strategies, novel (adjunctive) pharmacological molecules and state-of-the-art technological approaches. Based on a growing body of evidence that supports the technological advantages, the management of type 1 diabetes is changing substantially almost in real-time. Automated insulin delivery (AID) consists of a CGM that measures the glucose concentration, an insulin pump, and an algorithm that uses glucose concentration and prior insulin delivery data to control insulin delivery in a glucose-responsive manner is becoming the standard of care and is recommended for youth with diabetes were available in the latest ISPAD clinical guidelines. Recent randomized controlled trials have demonstrated the efficacy and safety of different control algorithms and have included different populations, including very young children with T1D and children with newly diagnosed T1D. These data were complemented with data from large multinational registries. Clinical outcomes in diabetes are unfortunately determined by disparities in socioeconomic status and consequently in inequities in diabetes care. Data from underserved countries and communities are critical in understanding barriers to technology use, including limited accessibility and reimbursement policies, and thus could help us develop targeted interventions to address these disparate outcomes.

17 | JOINT SYMPOSIUM IDF–ISPAD: HOW TO IMPROVE THE LONG-TERM DIABETES OUTCOME?

Life for a Child in collaboration with ISPAD, JDRF and IDF, has developed the T1D Index data simulation tool mapping the impact of T1D. The T1D index measures the human, public health, and economic impact of T1D throughout the world and at the country level. Incidence, prevalence and mortality are used to model estimates of new cases of T1D in a year by country, age group and risk of mortality and complications. There are approximately 9 million individuals estimated living with T1D globally. The global average for a person diagnosed with T1D at 10 years old will live 42 unburdened years but will have 32 healthy years lost due to early mortality, disability and complications. Timely diagnosis, access to insulin, test strips and new preventative therapies are strategies that could lead to 4 million fewer lives lost by 2040. Vascular complications and mortality rates remain a real challenge for young people with T1D requiring early prevention and detection for better outcomes. Data from the Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) showed that subclinical increases in albumin creatinine ratio (ACR) may provide a valuable tool to identify adolescents at higher risk of vascular complications. The keys to preventing complications during adolescence include good glycemic management, lifestyle interventions, angiotensin-converting enzymes (ACE) inhibitors, statins, and psychological and motivational interventions.

AUTHOR CONTRIBUTIONS

All authors wrote the draft and approved the final manuscript.

CONFLICT OF INTEREST

All the authors declare no other conflict of interests.

DATA AVAILABILITY STATEMENT

Not applicable.

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How to cite this article: Ng SM, Day H, Grundman JB, et al. ISPAD Annual Conference 2022 highlights. *Pediatr Diabetes*. 2022;23(8):1151-1156. doi:10.1111/pedi.13449

Received: 24 October 2022 | Accepted: 26 October 2022

DOI: 10.1111/pedi.13441

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Editorial

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KEYWORDS: adolescent, child, continuous glucose monitoring, glycemic targets, hypoglycemia, insulin, insulin pumps, limited resources, mortality, time in range, type 1 diabetes

The ISPAD 2022 clinical practice consensus guidelines were developed and completed during unprecedented times. First, due to the impact of the COVID-19 pandemic on people with diabetes and their families, diabetes professionals and care teams, our own families, health systems throughout the world, public health policy, and our individual work practices. Second, in the 4 years since the 2018 guidelines,[1] we have also experienced considerable evolution of technology for glucose monitoring, insulin delivery, and health care delivery. Moreover, in the 27 years since the first guidelines were published,[2] overall knowledge has profoundly impacted the management of diabetes, particularly in young children and youth, including wider use of insulin analogs, insulin pumps, continuous glucose monitoring (CGM), and automated insulin delivery devices. In recognition of these advances in diabetes care, the 2018 single guideline on diabetes technologies has been split into two separate guidelines for 2022: glucose monitoring and insulin delivery. The guideline on glycemic targets highlights the role of technology, with adoption of a unified fingerstick blood glucose level (BGL) target of between 4 and 10 mmol/L (70–180 mg/dl), which aligns with the target CGM time in range, along with a tighter fasting target range of 4–8 mmol/L (70–144 mg/dl).

Technological advances have also impacted prediction and prevention of T1D. While individuals with a first-degree relative with T1D have ~15-fold increased risk of T1D, approximately 85% of those with a new diagnosis do not have a family history of T1D. Hence, general population screening programs to determine T1D risk are expanding, and collaborative T1D networks testing interventions seeking to delay the disease process at all stages of disease are growing, including the use of CGM as a way to assess risk and track glycemia in these settings.[3]

For type 2 diabetes (T2D), follow-up of large cohorts from around the globe continue to inform the rates of co-morbidities and complications in youth-onset T2D, while pharmacologic therapies for the treatment of youth-onset T2D have expanded.[4] For monogenic diabetes, technological advances include the use of next-generation sequencing, which is now considered the best approach for early molecular diagnosis and to guide treatment, particularly for neonatal diabetes. For cystic fibrosis-related diabetes (CFRD), the guidelines have been updated to recommend insulin pumps and CGM for CFRD as appropriate and to address the effect of CF transmembrane conductance regulator (CFTR) modulator therapy (HEMT) on CFRD.

In all, there are 25 guidelines in 2022. They provide important updates on adolescence, ambulatory care, screening/management of complications and co-morbidities, CFRD, diabetic ketoacidosis, glycemic targets, education, epidemiology, exercise, hypoglycemia, monogenic diabetes, psychological care, preschool and school, Ramadan and other religious fasting, sick day management, stages of T1D, technology, and surgery. Overarching principles in all these new guidelines include use of technology, individualized person-centered care, and the impact of the COVID-19 pandemic, including a specific guideline in 2020.[5]

The great influenza pandemic began in 1918, before insulin was available to treat T1D; however, a century later we faced a new pandemic and still have problems with access to insulin, as well as BGL monitoring, insulin delivery devices, diabetes education, and adequate care. In 2021, it was estimated that 8.4 million people worldwide have T1D. Of these 1.5 million (18%) were younger than 20 years and 1.8 million (20%) of all people with T1D were from low-income and lower-middle-income countries.[6] Using a discrete-time illness-death model, the remaining life expectancy of a 10-year-old child diagnosed with T1D in 2021 was estimated to range from a mean of 13 years in low-income countries to 65 years in high-income countries.[6] Disparities in the social determinants of health and inequitable access to modern diabetes therapies remain significant barriers to achieving BGL targets and optimizing clinical outcomes. Disparities in care are addressed throughout the 2022 guidelines and a stand-alone comprehensive guideline is included on management of the child, adolescent, and young adult with diabetes in limited resource settings.

In total, 250 authors representing more than 55 countries contributed to the guidelines, including a person with diabetes or a carer, as well as a mix of early-career, mid-career, and senior clinicians. Most of the 2022 guidelines have new first authors. The guidelines benefited immensely from a project officer, Dr. Leena Priyambada, who has contributed to a more robust process of evidence grading[7] (Table 1) in collaboration with authors and co-editors, including three new co-editors (Linda DiMeglio, Farid Mahmud, and Loredana Marcovecchio). We also welcomed Joseph Wolfsdorf as guest editor. The writing teams have worked tirelessly, with meetings by zoom, often early morning or late at night. We sought conflict of interest disclosures during the process of writing the guidelines rather than at the time of publication, which was a recommendation from the 2018 guidelines and is now required by many other guideline developers. Finally, all authors followed guidance for use of language in the care of people with diabetes.[8]

TABLE 1 Evidence grading used in the 2022 ISPAD guidelines[7]

ADA evidence-grading system for "Standards of Medical Care in Diabetes"	
Level of evidence	**Description**
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, that is, "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case–control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

We wish to express our sincere thanks to all authors, ISPAD members, the ISPAD executive board over the past 4 years, Sylvia Lyon, and the editorial team at *Pediatric Diabetes*. This editorial is dedicated to Carlo Acerini, a co-editor of the 2018 guidelines, whose many recommendations have been implemented in the 2022 guidelines.

ACKNOWLEDGEMENT

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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How to cite this article: Craig ME, Codner E, Mahmud FH, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Editorial. *Pediatr Diabetes*. 2022;23(8):1157-1159. doi:10.1111/pedi.13441

Accepted: 9 November 2022
DOI: 10.1111/pedi.13454

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents

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KEYWORDS: classification, definition, epidemiology, incidence, Type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

This chapter serves as an update and replaces the 2018 ISPAD consensus guideline on definition, epidemiology, and classification of diabetes in children and adolescents.[1] It provides an evidence-based summary of current recommendations for defining and classifying diabetes in youth, as well as a description of the current knowledge about the epidemiology of this disease, emphasizing its heterogeneity.

2 | WHAT IS NEW OR DIFFERENT

- Diabetes in youth is a heterogeneous disorder in which clinical presentation and disease progression may vary considerably.
- Classification is important for determining therapy, but some individuals cannot be clearly classified at the time of diagnosis.
- Research has been conducted worldwide over the last several years combining genetic, clinical, and pathophysiological characteristics to better define the different types of diabetes in childhood and better understand the subtypes that are currently clustered into two most common types, type 1 diabetes (T1D) and type 2 diabetes (T2D).
- The goal of accurately defining the type of diabetes is to optimize personalized treatment approaches.
- Significant geographical variation in the incidence and prevalence of childhood T1D and T2D continues to be observed.

3 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Diagnostic criteria for all types of diabetes in children and adolescents are based on laboratory measurement of blood glucose levels

(BGL) and the presence or absence of symptoms. BGL testing with a glucometer should not be used to diagnose diabetes. **E**

- A marked elevation of the plasma glucose concentration confirms the diagnosis of diabetes, including a random plasma glucose ≥11.1 mmol/L (200 mg/dl) or fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl) in the presence of overt symptoms. **B**
- If blood or urine ketone levels are significantly increased, treatment is urgent and the child should be referred to a diabetes specialist on the same day to avoid the development of diabetic ketoacidosis (DKA). **A**
- The diagnosis of diabetes should not be based on a single BGL *in the absence* of overt symptoms. If the diagnosis is in doubt, continued observation with fasting and/or 2-h postprandial plasma glucoses and/or an oral glucose tolerance test (OGTT) may be required. **E** However, an OGTT is not needed and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria. **E**
- Hyperglycemia detected under conditions of stress, such as acute infection, trauma, surgery, respiratory distress, circulatory, rare metabolic conditions or other stress may be transitory and requires treatment but should not in itself be regarded as diagnostic of diabetes. **E**
- The differentiation between T1D, T2D, monogenic, and other forms of diabetes have important implications for both treatment and education. **E**
- Diagnostic tools, which may assist in confirming the diabetes type if the diagnosis is unclear, include:
  - diabetes-associated autoantibodies: glutamic acid decarboxylase 65 autoantibodies (GAD); tyrosine phosphatase-like insulinoma antigen 2 (IA2); insulin autoantibodies (IAA); and β-cell specific zinc transporter 8 autoantibodies (ZnT8). The presence of one of more of these antibodies confirms the diagnosis of T1D in children. **A**
- The possibility of other types of diabetes should be considered in the child who has negative diabetes-associated autoantibodies and: **B**
  - an autosomal dominant family history of diabetes (maturity onset diabetes of the young [MODY])
  - age less than 12 months and especially in first 6 months of life (neonatal diabetes mellitus [NDM])
  - mild-fasting hyperglycemia (5.5–8.5 mmol/L [100–150 mg/dl]), especially if young, non-obese, and asymptomatic (MODY)
  - a prolonged honeymoon period lasting more than 1 year or an unusually low requirement for insulin of ≤0.5 U/kg/day after 1 year of diabetes (MODY)
  - associated conditions such as deafness, optic atrophy, or syndromic features (mitochondrial disease)
  - a history of exposure to drugs known to be toxic to β-cells or cause insulin resistance (e.g., immunosuppressive drugs such as tacrolimus or cyclosporin; glucocorticoids or some antidepressants).
- Molecular genetic testing can help define the specific cause of diabetes and inform the appropriate treatment of children with suspected monogenic diabetes. **C** While certain clinical characteristics should alert clinicians to the possibility of monogenic diabetes, the absence of these characteristics does not exclude monogenic diabetes.

4 | DEFINITION AND DESCRIPTION

The term "diabetes mellitus" describes a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Inadequate insulin secretion and/or diminished tissue responses to insulin result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and deficient insulin action may coexist in the same individual.[2,3] While the etiology of diabetes is heterogeneous, most cases of diabetes can be classified into two broad etiopathogenetic categories (discussed later in further detail): T1D, characterized by the destruction of the ß-cells, usually by an autoimmune process, resulting in loss of endogenous insulin production, or T2D, characterized by the lack of an adequate insulin response in the presence of increasing insulin resistance. While T1D remains the most common form of youth-onset diabetes in many populations, especially those of European ancestry, T2D is an increasingly important global public health concern among youth, in particular adolescents, in high-risk ethnic populations as well as in those with obesity[4,5] (See ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 diabetes in children and adolescents). In addition, it is now recognized that people with monogenic diabetes, an autosomal dominant diabetes pattern first termed MODY, may make up 1%–6% of autoantibody negative individuals who may, initially, be considered to have either T1D or T2D with decreased insulin secretion.[6,7]

5 | DIAGNOSTIC CRITERIA FOR DIABETES IN CHILDHOOD AND ADOLESCENCE

Diagnostic criteria for diabetes are based on BGL measurements and the presence or absence of symptoms.[1–3] Different strategies can be used to measure BGL, including using a fasting plasma glucose (FPG) value, the 2-h plasma glucose (2-h PG) value during an OGTT, or hemoglobin A1c (HbA1c) criteria (Table 1) and in the absence of unequivocal hyperglycemia, diagnosis must be confirmed by repeat testing.

- Youth-onset diabetes usually presents with characteristic symptoms such as polyuria, polydipsia, nocturia, enuresis, and weight loss—which may be accompanied by polyphagia, fatigue, behavioral disturbance, including reduced school performance, and blurred vision. Impairment of growth and susceptibility to perineal candidiasis may also accompany chronic hyperglycemia. However, this is not always the case, particularly in youth with T2D.
- In its most severe form, DKA or (rarer) non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and, in the absence of effective treatment, death.

TABLE 1 Criteria for the diagnosis of diabetes mellitus

1. Classic symptoms of diabetes or hyperglycemic crisis with plasma glucose concentration ≥11.1 mmol/L (200 mg/dl).
Or
2. Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl). Fasting is defined as no caloric intake for at least 8 h.[a]
or
3. Two-hour postload glucose ≥11.1 mmol/L (≥200 mg/dl) during an oral glucose tolerance test (OGTT).[a]
The OGTT should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.
Or
4. HbA1c ≥6.5%.[b]
The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardized Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

[a]In the absence of unequivocal hyperglycemia, the diagnosis of diabetes requires two abnormal test results from the same sample or in two separate test samples.
[b]A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosis of T1D in children is unclear.

- If symptoms are present, point-of-care measurement of BGL and ketones using a meter, or urinary "dipstick" testing for glycosuria and ketonuria (if the former is not available) provides a simple and sensitive screening tool. If the BGL is elevated, then prompt referral to a center or facility with experience in managing children with diabetes is essential. Waiting another day, specifically to confirm the hyperglycemia, is unnecessary and if ketones are present in blood or urine, treatment is urgent, because DKA can evolve rapidly.
- A formal plasma glucose measurement is required to confirm the diagnosis. This should be obtained in a laboratory using an analytic instrument rather than a capillary glucose monitor. See Table 1 for fasting versus non-fasting BGL diagnostic cut-points.
- Scenarios where the diagnosis of diabetes may be unclear include:
- Absence of symptoms, for example, hyperglycemia detected incidentally or in children participating in screening studies
- Presence of mild/atypical symptoms of diabetes
- Hyperglycemia detected under conditions of acute infectious, traumatic, circulatory, or other stress, which may be transitory and should not be regarded as diagnostic of diabetes.
- In these situations, the diagnosis of diabetes should not be based on a single plasma glucose concentration and continued observation with fasting and 2-h postprandial BGL and/or an OGTT may be required to confirm the diagnosis.
- An OGTT is usually not required and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria. It is rarely indicated for making the diagnosis of T1D in childhood and adolescence but may be useful in diagnosing other forms such as T2D, monogenic diabetes, or cystic fibrosis-related diabetes (CFRD). If doubt remains, periodic OGTT retesting should be undertaken until the diagnosis is established. It is important that people consume a mixed diet with at least 150 g of carbohydrate on the 3 days prior to oral glucose tolerance testing.[3,8] Fasting and carbohydrate restriction can falsely elevate BGL with an oral glucose challenge.
- HbA1c can be used as a diagnostic test for diabetes, in particular to test for prediabetes or T2D in youth[4]; providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present, which preclude its accurate measurement.[3,4] Moreover, the validity of HbA1c as a measure of average BGLs is affected by hemoglobinopathies, certain forms of anemia, or any other condition that affects normal red blood cell turnover. These conditions may follow specific ethnic and geographic distributions and thus is a critical consideration in areas of iron deficiency and anemia. For conditions with abnormal red cell turnover, such as anemias from hemolysis and iron deficiency, as well as cystic fibrosis, the diagnosis of diabetes must exclusively employ BGL criteria.[3] See ISPAD 2022 Consensus Guidelines Chapter 5 on Management of Cystic Fibrosis-Related Diabetes in children and adolescents.

In at-risk cohort studies, however, a rise in HbA1c within the normal range is frequently observed among individuals who subsequently progress to T1D.[9] Data from four separate prospective studies of high-risk subjects <21 years of age (the Diabetes Prevention Trial–Type 1 (DPT-1), The Environmental Determinants of Diabetes in the Young (TEDDY), Trial to Reduce IDDM in the Genetically at Risk (TRIGR), and T1D TrialNet Natural History Study (HbA1C) measured within 90 days of a diagnostic OGTT or fasting PG ≥126 mg/dl) show that HbA1C ≥6.5% is a highly specific but not a sensitive early indicator of T1D diagnosed by OGTT or asymptomatic hyperglycemia.[10] HbA1c when monitored in individuals longitudinally, even if within the normal range, maybe have added value in T1D prediction.[11] Point-of-care assays for HbA1c are not recommended for diagnostic purposes.

6 | IMPAIRED GLUCOSE TOLERANCE AND IMPAIRED FASTING GLUCOSE

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes. IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation or different stages in the progression of dysglycemia.[3] IFG is a measure of disturbed carbohydrate metabolism in the basal state, whereas IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load. IFG and IGT are not clinical entities in their own right; individuals with IFG and/or IGT are referred to as having "prediabetes," indicating their relatively high risk

for development of diabetes and cardiovascular disease, especially in the context of obesity.[12] Diagnostic criteria for prediabetes and diabetes in children, including FPG, OGTT, and HbA1c 5.7%–6.4% (39–47 mmol/mol) are the same for the pediatric and adult population (Table 1). These criteria are extrapolated from adults, and the epidemiological studies that formed the basis for these definitions did not include pediatric populations. Therefore, the exact relevance of these definitions for pediatric populations remains unclear until more data become available.[4] Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal HbA1c levels, and those with IGT may manifest hyperglycemia only when challenged with an OGTT. Screening with fasting glucose, OGTT, or HbA1C is an acceptable approach but the interpretation of the results should be based on sound clinical judgment, recognition of the strengths and weaknesses of each test, and the facilities and resources available.

Each of the tests mentioned has some variability, so it is possible that a test yielding an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point.[3,13] One of the possibilities could be that the BGL samples are kept at room temperature and not centrifuged promptly. Because of the potential for pre-analytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If individuals have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with them and repeat the test in 3–6 months.

7 | STAGING OF TYPE 1 DIABETES

Characterization of the underlying pathophysiology of T1D from prospective studies around the world has given rise to what is described as the staging of type 1 diabetes. Three distinct stages of T1D can be identified and serve as a framework for future research and regulatory decision-making.[14] This staging is based on the presence of ß-cell autoantibodies and dysglycemia as predictors of clinical diabetes (stage one characterized by multiple β-cell autoantibody positivity with normal glucose, stage 2 multiple β-cell autoantibody positivity with dysglycaemia, and stage 3 meeting criteria for clinical diagnosis of T1D) and is described in detail in the ISPAD 2022 Consensus guidelines Chapter 2 on Stages of Diabetes.

8 | CONFIRMING THE DIAGNOSIS

Unless there is a clear clinical diagnosis (e.g., symptomatic individuals with clear hyperglycemia) diagnosis requires two abnormal screening test results, either from the same sample (two different tests) or in two separate test samples.[3] If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. If two different tests (such as HbA1c and FPG) are both above the diagnostic threshold when analyzed from the same sample or in two different test samples, this also confirms the diagnosis. On the other hand, if an individual has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of the possibility of HbA1c assay interference. The diagnosis is made based on the confirmatory screening test.

9 | CLASSIFICATION OF DIABETES AND OTHER CATEGORIES OF GLUCOSE REGULATION

It was at the end of the 1970s that the scientific community established formal diabetes classifications, which could be used to guide therapy. The first, introduced in 1976 by the United States National Diabetes Data Group[15] and endorsed by the World Health Organization Expert Committee on Diabetes Mellitus,[16] was based on the need for insulin therapy for survival. The juvenile onset, usually ketotic type, was renamed insulin dependent diabetes mellitus (IDDM), while the adult onset, usually non-ketotic type, was termed non-insulin dependent diabetes (NIDDM). The classification was revised in 1997 based upon pathophysiology rather than insulin requirements, facilitated by the distinction between the autoimmunity driving insulin deficiency in IDDM and insulin resistance contributing to NIDDM. Absolute insulin deficient states became known as T1D, with NIDDM, usually associated with insulin resistance, renamed T2D.

The current etiological classification of diabetes is shown in Table 2, which is based on the ADA classification.[3] Today, most people with diabetes are grouped into two main types: T1D, characterized by the destruction of the ß-cells, usually by an autoimmune process resulting in loss of endogenous insulin production, or T2D, characterized by the lack of an adequate insulin response in the presence of increasing insulin resistance. The type of diabetes assigned to a young person at diagnosis is typically based on their characteristics at presentation; however, increasingly, the ability to make a clinical diagnosis has been hampered by factors including the increasing prevalence of overweight in young people with T1D[17,18] and the presence of DKA in some young people at diagnosis of T2D.[19,20] In addition, the presentation of a familial form of mild diabetes during adolescence should raise the suspicion of monogenic diabetes, which accounts for 1% to 6% of pediatric diabetes cases.[6,7,21–23]

Using the etiologic approach to classification of diabetes types in youth based on the 1997 ADA framework, the majority of youth in the US-based SEARCH for Diabetes in Youth Study fell into either the autoimmune plus insulin sensitivity (54.5%) or non-autoimmune plus insulin resistance categories (15.9%) consistent with traditional descriptions of type 1 or T2D.[24] The remaining groups represented obesity superimposed on T1D (autoimmune plus insulin resistance, 19.5%) or atypical forms of diabetes (non-autoimmune plus insulin sensitivity, 10.1%), which require further characterization, including genetic testing for specific monogenic defects.[25] As the prevalence of childhood obesity continues to increase in the general population and

TABLE 2 Etiological classification of diabetes

I. Type 1
β-cell destruction, usually leading to absolute insulin deficiency
Immune mediated (characterized by presence of one or more autoimmune markers)
Idiopathic
II. Type 2
Insulin resistance with relative insulin deficiency and subsequent hyperglycemia
III. Other specific types
A. Common forms of monogenic diabetes[a]
MODY
• HNF4-A MODY
• GCK MODY
• HNF1A MODY
• HNF1B MODY
Neonatal diabetes
• KCNJ11
• INS
• ABCCB
• 6q24 (PLAGL1, HYMA1)
• GATA6
• EIF2AK3
• FOXP3
B. Genetic defects in insulin action
INSR
Congenital generalized lipodystrophy
Familial partial lipodystrophy
PIK3R1 (Short Syndrome)
C. Diseases of the exocrine pancreas
Pancreatitis
Trauma/pancreatectomy
Neoplasia
Cystic fibrosis-related diabetes
Hemochromatosis
Transfusion-related iron overload
D. Endocrinopathies
Acromegaly
Cushing's syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
Somatostatinoma
E. Drug- or chemical-induced
Insulin resistance and deficiency
• Glucocorticoids
• Nicotinic acid
• Atypical antipsychotics
• Protease inhibitors (first generation)
• Statins
Insulin deficiency
• β-blockers
• Calcineurin inhibitors
• Diazoxide
• Phenytoin
• L-asparaginase
• Pentamidine
• Thiazide diuretics
Insulin resistance
• β-adrenergic agonists
• Growth hormone
F. Infections
Congenital rubella
Enterovirus
Cytomegalovirus
G. Uncommon forms of immune-mediated diabetes
Anti-insulin receptor antibodies
Polyendocrine autoimmune deficiencies APS I and II
H. Other genetic syndromes sometimes associated with diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
Friedreich's ataxia
Myotonic dystrophia
Porphyria
Prader–Willi syndrome
IV. Gestational diabetes mellitus (GDM)

Abbreviations: HNF, hepatic nuclear factor; GCK, glucokinase.
[a]See also ISPAD 2022 Guideline on Monogenic Diabetes.

in youth with diabetes, great care must be taken to correctly differentiate diabetes type in the setting of obesity,[26] particularly with regards to youth with T1D and antibody negative diabetes who show clinical signs of T2D such as obesity and insulin resistance.[27,28]

After the initial step of diagnosing diabetes, the differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both therapeutic decisions and educational approaches. Individuals with any form of diabetes may or may not require insulin treatment at various stages of their disease. Such use of insulin does not, of itself, classify the diabetes type. Diabetes-associated autoantibodies are an important diagnostic tool. The presence of GAD, IA2, IAA, and/or ZnT8 confirms the diagnosis of T1D in children.[28] Measurements of autoimmune markers are useful in confirming T1D in those where presentation is not clear, in particular obese adolescents.

The possibility of other types of diabetes should be considered in the child who does not have diabetes-specific autoantibodies and:

- an autosomal dominant family history of diabetes in three generations with onset before age 35 years.
- diabetes diagnosed in the first 12 months of life, especially the first 6 months (NDM).
- mild-fasting hyperglycemia (5.5–8.5 mmol [100–150 mg/dl]); that is, IFG, especially if young, non-obese, and asymptomatic.
- associated conditions such as deafness, optic atrophy, or syndromic features (mitochondrial disease).
- a history of exposure to drugs known to be toxic to β-cells (cyclosporine or tacrolimus)[29] or cause insulin resistance (glucocorticoids and certain antidepressants).[30,31]

T2D and monogenic diabetes are more completely discussed in the ISPAD guidelines on these conditions. See the ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 diabetes in children and adolescents and Chapter 4 on The diagnosis and management of monogenic diabetes in children and adolescents. Regardless of the type of diabetes, however, the child who presents with severe hyperglycemia, ketonemia, and metabolic derangements will initially require insulin therapy to reverse the metabolic abnormalities.

Some forms, including specific drug-, hormone-, or toxin-induced forms of diabetes, are less commonly observed in young people. Atypical forms of diabetes may occur in older children, adolescents, and young adults including ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibro-calculous pancreatic disease.[32,33]

10 | PATHOGENESIS OF T1D

T1D is characterized by chronic immune-mediated destruction of pancreatic β-cells, leading to partial, or in most cases, absolute insulin deficiency. In the majority of cases, autoimmune-mediated pancreatic β-cell destruction occurs at a variable rate and is influenced by different factors, including genes, age, and ethnicity.[34,35] New insights into youth at risk for developing T1D suggest that early disease is a continuum that progresses through distinct identifiable stages prior to the appearance of clinical symptoms.[14] Youth progress through three stages at variable rates: stage 1, which can last for months to many years, is characterized by the presence of β-cell autoimmunity with normoglycemia and a lack of clinical symptoms; stage 2 progresses to dysglycemia but remains asymptomatic, and stage 3 is defined as the onset of symptomatic disease.[14] The phases of diabetes are discussed in ISPAD 2022 Consensus Guidelines Chapter 2 on Stages of Type 1 Diabetes in Children and Adolescents.

The etiology of T1D is multifactorial; however, the specific roles for genetic susceptibility, environmental factors, the immune system, and β-cells in the pathogenic processes underlying T1D remain unclear.

The overall risk of T1D in the general population is 0.4%. Relatives of persons with T1D have a higher risk. In siblings, the lifetime risk is 6%–7%; 1.3%–4% in children of a mother with T1D, and 6%–9% in those with a father with T1D.[36,37] While the risk of T1D in non-identical twins is similar to that of siblings, it exceeds 70% in identical twins with long-term follow-up.[38,39] Additional evidence for the contribution of genetic factors to the etiology of T1D is the rare occurrence of autoimmune diabetes in association with mutations affecting key genes that regulate immune function. An example of this is the autoimmune polyglandular syndrome type 1 (APS1) caused by mutations in the autoimmune regulator (*AIRE*) gene, which is critical for the establishment of immunological self-tolerance.[40,41]

Studies predominantly from European ancestry populations have shown that susceptibility to T1D is determined by multiple genes. The HLA region on chromosome 6p21 accounts for approximately 30%–50% of the familial aggregation of T1D, and its association with T1D has been known for over 40 years.[42,43] The strongest association is with HLA DR and DQ. HLA DR and DQ are cell surface receptors that present antigens to T-lymphocytes. Both DR and DQ are alpha-beta heterodimers. The DR alpha chain is encoded by the DRA locus, and the DR beta chain is encoded by DRB loci. Similarly, DQA1 and DQB1 loci encode the alpha and beta chains, respectively, of the DQ molecule. The DR and DQ loci are highly linked to each other and, to a lesser degree, to other HLA loci.[44,45]

The highest-risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and T1D[45]; however, <10% of those with HLA-conferred diabetes susceptibility genes progress to clinical disease.[46] As the highest risk HLA allele combination is relatively rare (<5%) in European populations, the majority of T1D cases are associated with other combinations of these alleles that confer more moderate risk but in aggregate are more common than ¾.[47] For example, DRB3, DRB4, and DRB5 alleles modify the risk conferred by DRB1.[48] Although the strength of the association is lower than with HLA DR and DQ, HLA-DPB1 and DPA1 are also associated to T1D.[49]

The remaining genetic risk for T1D can be attributed to the other non-HLA genes or loci identified that contribute smaller effects to disease risk. Genome-wide association studies (GWAS) have identified more than 60 risk loci.[44] Of these, the highest non-HLA genetic contribution arises from the insulin gene (*INS*) on chromosome 11p15,[50,51] protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*), on chromosome 1p13,[52] cytotoxic T-lymphocyte associated protein (*CTLA-4*),[53] which is a negative regulator of cytotoxic T cells, and IL2RA genes,[54] all of which are involved in, or contribute to, immune regulation in various immune cell populations and/or the pancreatic β-cell.

Other genes not directly involved in immune function have been shown to possibly contribute to diabetogenesis in a subset of individuals with islet autoimmunity. Genetic variants in the transcription factor 7 like-2 (*TCF7L2*) locus are the strongest genetic factor in T2D.[55] Although this locus is not associated with T1D overall, persons with T1D with milder autoimmunity, as suggested by the expression of a single islet autoantibody and/or absence of high-risk HLA types, are more likely to carry the T2D-associated *TCF7L2* genetic variant compared to persons with T1D with stronger autoimmunity.[56]

One of the current challenges is how to integrate the wealth of knowledge about T1D genetics and apply it meaningfully for diagnosis

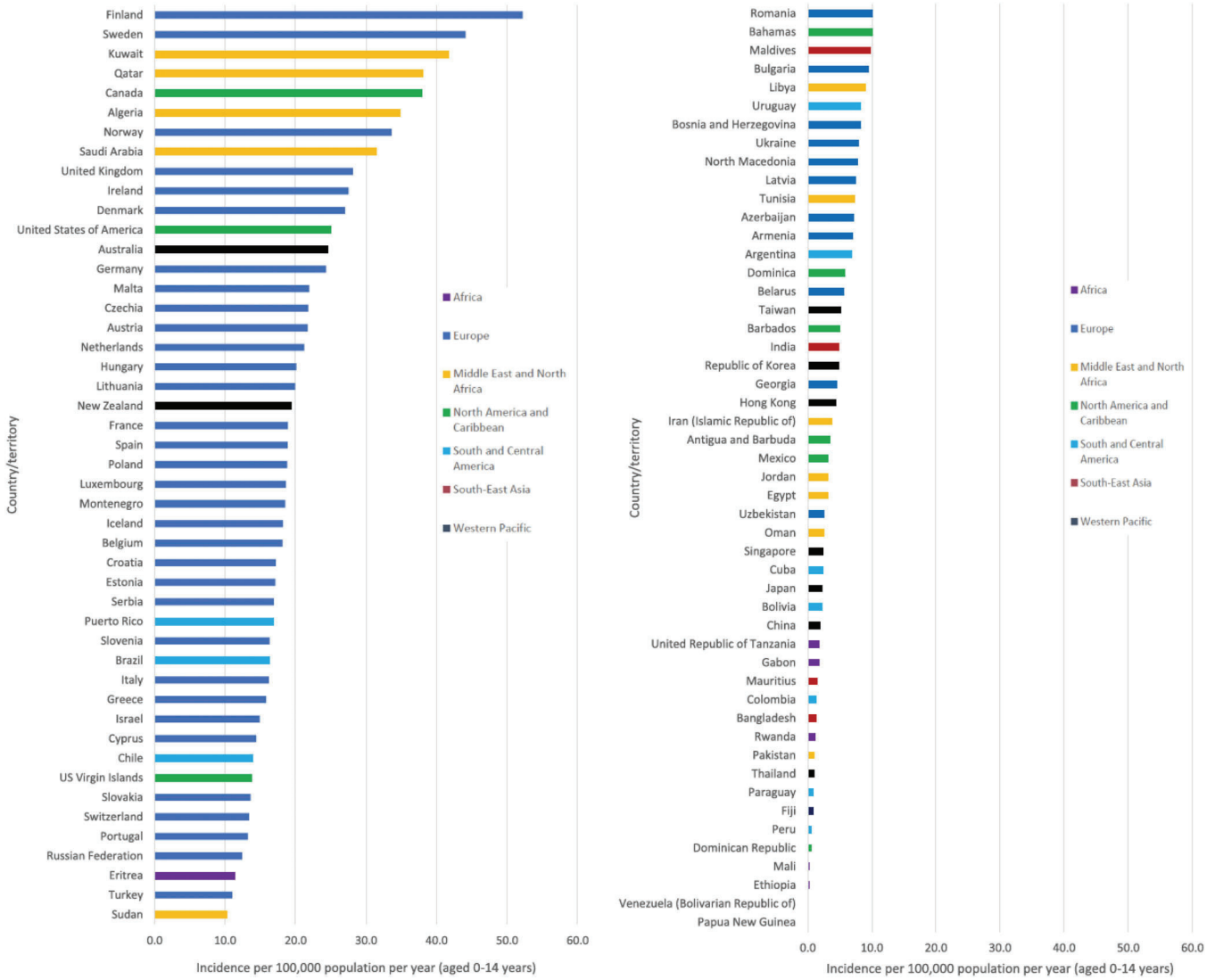

FIGURE 1 Published age-standardized incidence of T1D reported in children aged 0–14 years.[2] Reprinted from Diabetes Research and Clinical Practice, Volume 183, Graham D. Ogle, Steven James, Dana Dabelea, Catherine Pihoker, Jannet Svennson, Jayanthi Maniam, Emma L. Klatman, Chris C. Patterson, *Global estimates of incidence of T1Din children and adolescents: Results from the International Diabetes Federation Atlas, 10th edition*, Copyright (2022) with permission from Elsevier (License Number: 5264490510252)].

and risk assessment. Recent work has studied the use of T1D genetic risk scores for distinguishing persons with T1D from other forms of diabetes[57,58] among them the DAISY Study,[59–61] the BABYDIAB study[62,63] and, more recently, the Exeter group have developed a T1D Genetic Score to identify individuals who became insulin dependent among young adults with diabetes[25] and discriminate T1D from monogenic diabetes.[57] This score was developed studying participants in the Wellcome Trust Case Control Consortium ($n = 3887$), in which it was highly discriminative of T2D. This score was validated in the South West England Cohort, where it predicted insulin deficiency in a group of 20–40-year-old adults with diabetes ($n = 223$, excluded monogenic and secondary diabetes). A more recently developed T1D GRS2[58] has shown improved prediction of type 1 diabetes[58,64] and also demonstrated improved discrimination of type 1 from type 2 diabetes in USA youth self-reporting as either Black or Hispanic.[65]

As more genetic association data emerges from non-European ancestries,[66] there is an outstanding question as whether ancestry specific scores, or combined transancestry scores potentially with adjustable score thresholds per ancestry, will be the optimal method to aggregate genetic risk for clinical applications.

The environmental triggers (infectious, nutritional, obesity, changes in the microbiome, chemical) which are thought to be associated to T1D and pancreatic β-cell destruction remain largely unknown, but the process of β-cell destruction usually begins months to years before the manifestation of clinical symptoms.[67–73] Enterovirus infection during pregnancy, infancy, childhood, and adulthood has been associated with development of both islet autoimmunity and many populations,[74,75] particularly when infection occurs early in childhood,[76] and enteroviruses have been detected in the islets of persons with diabetes.[77–79] Congenital rubella syndrome has been

linked to the subsequent development of T1D.[80] There is a paucity of data to support the role of other viruses, such as CMV, mumps, Influenza, rotavirus, and HIN1 in the development of T1D.[71]

11 | EPIDEMIOLOGY OF TYPE 1 DIABETES

T1D is the most common form of diabetes in children and adolescents, accounting for >90% of childhood diabetes in most westernized countries, but other types of diabetes, including T2D and monogenic diabetes, also occur.[81] Worldwide, T1D is also one of the commonest chronic diseases of childhood. In 2021, there were an estimated 108,300 children and adolescents aged less than 15 years newly diagnosed with type 1 diabetes, and 651,700 children and adolescents living with the condition worldwide.[82,83]

Significant geographical variation in the incidence of childhood T1D continues to be observed (Figure 1),[82–85] ranging from 1.9 to 2.2 per 100,000 person years in China[86] and Japan,[84,87] respectively, to 52.2 per 100,000 in Finland,[88] where the highest incidence has been observed for several decades.[89] Notably, four of the top 10 countries with the highest incidence for childhood T1D listed in the latest edition of the International Diabetes Federation Global Atlas of Diabetes include the non-European populations of Kuwait, Qatar, Saudi Arabia, and Algeria.[83] While considering global patterns in childhood T1D, it is important to note that despite recent improvements in data availability from low-middle income countries,[90,91] most of the available global T1D incidence data is from highly developed countries,[83] and the relatively low incidence of T1D in low-middle income countries needs to be evaluated in the context of their higher mortality and lower case ascertainment rates.[82,92]

In addition to large differences in incidence between countries, significant geographic variation has also been observed within countries themselves.[93–97] Studies in heterogenous populations have observed significant differences in incidence by race/ethnicity, which could contribute to geographical variation within and between countries. For example, in the United States SEARCH study, a higher incidence of T1D has been consistently observed in non-Hispanic white compared to Hispanic, Black, and American Indian youth aged <20 years.[98,99]

However, a study of genetically similar populations living in countries with different environments found that these populations had different incidence rates of childhood T1D[93,100] suggesting that a combination of both environmental and 21eneticc differences are more likely to explain the geographical variation. Inconsistent findings have been reported on the association between higher childhood T1D incidence and environmental characteristics such as degree of urbanicity, population density, neighborhood socioeconomic status, higher latitude, or distance from the equator.[94–97,100] Factors underlying geographical differences in the incidence of childhood T1D remain poorly understood.[101,102]

Overall, there is no significant difference in the incidence of childhood T1D by sex,[103–105] although a slightly higher incidence has been reported in boys in some moderate-high incidence populations.[90,106] However, above the age of 15 years, there is a male preponderance in T1D incidence.[107]

The incidence of childhood T1D varies by age, with many populations reporting a peak age of onset in 10–14-year olds.[91,92,105,106] However, in Finland, the peak age of onset is 5–9 years, and in some countries, a decreasing peak age of incidence has been observed in recent years.[82]

Despite wide global variation in the incidence of childhood onset T1D, increasing trends in incidence have been observed in most populations, with incidence increasing by an average of 3%–4% per year.[82,91,97,108] However, more recently, a slowing of this increasing trend and a plateauing of incidence has been reported by several moderate-high incidence countries including Finland,[88] Austria,[109] Germany,[110] Ireland,[106] Australia,[105] New Zealand,[111] Sweden.[107,108] Intriguingly, a sinusoidal pattern with 4–6-year intervals between peak incidence years has been reported in some European countries and Australia,[17,108,112,113] with no explanation for this non-linear pattern. Of note, the cyclical pattern in incidence observed in these countries is distinct from the well-established seasonality of incidence of childhood T1D, with annual peaks in incidence having long been observed in the cooler autumn and winter months.[106,114–117]

Further analysis of temporal trends in the incidence of childhood T1D by sex, age group at diagnosis and race/ethnicity show additional complexity to the changing epidemiology of childhood T1D. In many populations a similar increasing trend has been observed in both boys and girls and across all age groups.[82] However, a higher rate of increase has been reported in girls compared to boys in Ireland, especially in 10–14-year olds, compared to younger age groups.[106] Since early reports in the late 1990s of a higher rate of increase being observed in those under 5 years old,[118,119] a decreasing incidence rate in the youngest age group has recently been reported in Finland,[88] Austria,[109] and Australia.[105] The decreasing incidence trend in 0–4-year olds has been suggested to account for the levelling off in the overall incidence of childhood T1D being observed in Finland[88] and Austria.[109] Interestingly, the United States SEARCH study, one of the few global studies to examine incidence rate trends of youth-onset T1D by race/ethnicity, recently showed that the rate of increase is highest in Black and Hispanic youth, compared to non-Hispanic White youth.[99] Differences in incidence by ethnicity have also been observed in New Zealand.[111]

The epidemiology of childhood T1D continues to change and evolve, with marked differences continuing to be observed between different countries and demographic groups within countries. The systematic, harmonized collection of robust, population-based data is vital for the ongoing monitoring of global patterns and trends in childhood T1D.

For example, recent epidemiological studies conducted during the COVID-19 pandemic have optimized the use of well-established robust data collection methods and enabled rapid reporting of contemporary changes in T1D epidemiology. An increased incidence of pediatric onset T1D occurring concurrent with the COVID-19 pandemic has been reported in Germany and the United States,[120–122] providing novel biologically plausible mechanistic insights into the etiology and/or clinical presentation of the condition.[123] It is possible that the increase in incidence might be due to concurrent illness

precipitating clinical diagnosis of T1D rather than a change in the risk of developing T1D as this often take years.

These data and analysis of incidence trends and patterns is essential for informing local health service planning and models of care in each country, and for providing contemporary population-specific clues to help further the understanding of potentially modifiable environmental determinants of childhood T1D and inform efforts to reduce its incidence. Recently, a new model, the Type 1 Diabetes Index, was developed based on available data to estimate T1D prevalence, incidence, associated mortality and life expectancy. Predictions for 2040, based on findings in 2021, include an increase in prevalent cases from 8.4 million individuals worldwide to 13.5–17.4 million, with the largest relative increase in low-income and lower-middle-income countries. This tool could play a critical role to support health delivery, advocacy, and funding decisions for T1D.[124]

Future research into the epidemiology of early life factors and their association with childhood T1D incidence[125] and the application of new methods and technologies[126] will provide novel knowledge and complement the ongoing surveillance of childhood T1D incidence.

12 | PATHOGENESIS OF T2D

T2D is characterized by hyperglycemia caused by insulin resistance, and relative impairment in insulin secretion due to β-cell dysfunction either as inborn genetic defect of acquired from glucose toxicity, lipotoxicity, or other mechanisms. The etiology includes contribution by genetic and physicologic components, lifestyle factors such as excess energy intake, insufficient physical activity, and increased sedentary behavior.[4] The pathogenesis of type 2 diabetes is variable between individuals and complicated by heterogeneity in the degree of insulin resistance and deficiency, genetic, and environmental influences, and comorbidities including hypertension, hyperlipidemia, and obesity.[127] Peripheral insulin resistance is a key feature that occurs early in the disease course, and initially is compensated by increased insulin secretion reflected in hyperinsulinemia.[127] Sustained hyperglycemia over time results in β-cell exhaustion and declining insulin secretion (glucose toxicity). Type 2 diabetes in youth is typically clinically characterized by insulin resistance, as well as other features of metabolic syndrome, which are commonly present, including hypertension, hyperlipidemia, acanthosis nigricans, fatty liver disease, and polycystic ovary disease.[128] Further details on the pathogeneis, and management are discussed in ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes in Children and Adolescents.

13 | EPIDEMIOLOGY OF T2D

Once a rare disease in youth, T2D is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at-risk populations. Worldwide incidence and prevalence of T2D in children and adolescents vary substantially among countries, age categories and ethnic groups.[129–134] The incidence and prevalence of T2D are highest among youth from a minority race/ethnicity,[99] likely because of many factors, including genetics, metabolic characteristics, cultural/environmental influences, and quality of and access to health care.[135,136]

14 | MONOGENIC DIABETES

A familial form of mild, non-ketotic diabetes presenting during adolescence or early adulthood[137,138] originally termed MODY, is now recognized as a group of disorders which result from dominantly acting heterozygous mutations in genes important for the development or function of β-cells.[138,139] Despite the classical description of MODY as a disorder with onset before 25 years of age, autosomal dominant inheritance, and non-ketotic diabetes mellitus,[139,140] it is clear that there is considerable overlap in the presentations of T1D, T2D, and monogenic diabetes. As a result, monogenic diabetes may be misdiagnosed and treated incorrectly. The etiology, diagnosis and management of monogenic diabetes are described in detail in the ISPAD 2022 Consensus Guidelines Chapter 5 on The diagnosis and management of monogenic diabetes in children and adolescents.

15 | NEONATAL DIABETES MELLITUS

T1D rarely presents in the first year of life, particularly before age 6 months.[141,142] In in very young infants, under the age of 6 months, it is likely that over 80% have a monogenic cause,[143] with the most common one being β cell/potassium channel mutations. A small minority of NDM is accounted for by rate genetic mutations in immune system genes including mutations in the transcription factor FOXP3 as part of the immune-dysregulation poly-endocrinopathy enteropathy X-linked (IPEX) syndrome.[144] Genetic testing in those diagnosed under age 6 months is indicated, likely to find the cause, and may change treatment.[144–147] Further details of the genetic basis of NDM are provided in the ISPAD 2022 Consensus Guidelines Chapter 5 on The diagnosis and management of monogenic diabetes in children and adolescents.

16 | MITOCHONDRIAL DIABETES

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterized by progressive non-autoimmune β-cell failure.[148,149] Transmission of maternal mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition.[150,151] Mitochondrial diabetes may present with variable phenotypes, ranging from acute onset with or without DKA, to a more gradual onset resembling T2D. The disease typically presents in young adults, but can occur in children and adolescents, who have a lower prevalence of hearing loss compared with adults.[152]

17 | CYSTIC FIBROSIS-RELATED DIABETES

Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity associated with cystic fibrosis (CF). The pathophysiology of CFRD is primarily due to insulin deficiency, along with glucagon deficiency and variable insulin resistance (particularly during acute illness, secondary to infections and medications such as bronchodilators and glucocorticoids). Other contributory factors include the need for high caloric intake, delayed gastric emptying, altered intestinal motility, and liver disease.[153] CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycemia followed by IGT and finally diabetes. Early CFRD is characterized by normal fasting BGL, but over time fasting hyperglycemia develops. CFRD typically presents in adolescence and early adulthood[154] but may occur at any age. The presentation may be asymptomatic, insidious, associated with poor weight gain[155] or precipitated by insulin resistance associated with infection/use of glucocorticoids. Detection rates for CFRD vary with screening practices.[156] The onset of CFRD is defined as the date a person with CF first meets diagnostic criteria for diabetes, even if hyperglycemia subsequently abates. The onset of CFRD is a poor prognostic sign and is associated with increased morbidity and mortality reported prior to implementation of routine screening for CFRD and early use of insulin therapy.[157] Poorly controlled CFRD interferes with immune responses to infection and promotes protein catabolism.[156,158] Annual screening for CFRD should commence at least by age 10 years in all persons with CF who do not have CFRD. Screening should be performed using the 2-h 75 g (1.75 g/kg) OGTT.[3] A more comprehensive discussion on CFRD can be found in ISPAD 2022 Consensus guidelines Chapter 5 on Cystic Fibrosis Related Diabetes in Children and Adolescents.

18 | HEMOCHROMATOSIS AND DIABETES

Hemochromatosis is an inherited or secondary disorder caused by excessive iron storage leading to multiple organ damage.[159] Primary hemochromatosis is an autosomal recessive disease presenting as liver cirrhosis, cardiac dysfunction, hypothyroidism, diabetes, and hypogonadism. Secondary hemochromatosis may develop in individuals who have received multiple red blood cell transfusions.[160] Diabetes associated with hemochromatosis is primarily due to loss of insulin secretory capacity by damaged β-cells with insulin resistance playing a secondary role. The prevalence of diabetes in this population is not well characterized and has likely been underestimated.[161]

19 | DIABETES INDUCED BY DRUGS AND TOXINS

A range of pharmacological agents impair insulin secretion (e.g., propranolol), and/or action (e.g., glucocorticoids, antipsychotic agents), while others (e.g., calcineurin inhibitors, pentamidine) can cause permanent β-cell damage.[3,162–164]

In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral edema. The additional stress of surgery may add to the drug-induced insulin resistance and cause a relative insulin deficiency, sufficient to cause transient diabetes. Hyperglycemia may be exacerbated if large volumes of intravenous dextrose are given for management of diabetes insipidus. An intravenous insulin infusion is the optimal method to control the hyperglycemia, which is usually transient. In oncology, protocols which employ L-asparaginase, high dose glucocorticoids, cyclosporin, or tacrolimus (FK506) may be associated with secondary or transient diabetes. L-asparaginase usually causes a reversible form of diabetes.[165] Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction.[29] Often the diabetes is cyclical and associated with the chemotherapy cycles, especially if associated with large doses of glucocorticoids. Immune checkpoint inhibitors can cause a special form of autoimmune diabetes characterized by a rapid loss of ß-cell function.[166] Following organ transplantation, diabetes most frequently occurs with the use of high dose glucocorticoids and tacrolimus; the risk is increased in individuals with preexisting obesity.[167–169] Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidone, quetiapine, and ziprasidone, which may be associated with weight gain. In children and adolescents, use of antipsychotics was associated with a more than 3-fold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose.[170] Among Canadian youth with medication-induced diabetes, risk factors for T2D (family history of T2D, obesity, non-Caucasian ethnicity, acanthosis nigricans) were less commonly observed than in youth with T2D.[171]

20 | STRESS HYPERGLYCEMIA

Hyperglycemia that occurs as a response to stress is transient in individuals without known diabetes. Stress hyperglycemia has been reported in up to 5% of children presenting to an emergency department, in association with acute illness or sepsis; traumatic injuries, febrile seizures, burns, and elevated body temperature (>39°C).[172–175]

However, the incidence of severe hyperglycemia (≥16.7 mmol/L or 300 mg/dl) was <1% and almost two-thirds of individuals had received interventions influencing glucose metabolism before evaluation, suggesting the etiology may at least in part be iatrogenic.[176]

The reported incidence of progression to overt diabetes varies from 0% to 32%.[177–183] Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness.[184] As would be expected, testing for diabetes-associated autoantibodies had a high positive and negative predictive value for the development of T1D in children with stress hyperglycemia.[181] In children who have sustained severe burns, insulin resistance may persist for up to 3 years later.[174]

21 | CONCLUSION

Diabetes in youth is a heterogeneous disorder in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but in some individuals, overlapping clinical characteristics do not allow for diabetes type to be determined at the time of diagnosis. Progress has been made in understanding the pathophysiology as well as genetic characteristics of the different types of diabetes in childhood and markers are available to facilitate this task. Research has been conducted worldwide over the last several years combining genetic, clinical, and pathophysiological characteristics to better define the different types of diabetes in childhood, which is getting us closer to the goal of optimizing personalized treatment approaches. The challenge in the years ahead is to ensure that these advances reach all youth across the world.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Libman I, Haynes A, Lyons S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8): 1160-1174. doi:10.1111/pedi.13454

Received: 26 August 2022 | Accepted: 29 August 2022

DOI: 10.1111/pedi.13410

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents

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1 | INTRODUCTION

This guideline serves as an update to and replacement of the 2018 ISPAD consensus guideline on stages of type 1 diabetes (T1D). Herein, we provide an evidence-based summary of recommendations for screening children for T1D risk and discuss potential opportunities for clinical trials designed to delay progression to Stage 3 T1D and preserve beta cell function in those with Stage 3 disease. We again use the American Diabetes Association's metrics for grading evidence from A through E. We acknowledge that priorities may differ in low-income countries that may not be able to offer screening.

2 | WHAT IS NEW OR DIFFERENT

- Stages 1, 2, 3, and 4 T1D are being used in clinical, research, and regulatory settings.
- General population screening programs to determine T1D risk are expanding.
- Collaborative T1D networks testing interventions seeking to delay the disease process at all stages of disease are growing.
- Tools to predict T1D and response to interventions are improving.
- Anti-CD3 monoclonal antibody (teplizumab) is being evaluated by the U.S. Food and Drug Administration (FDA) for use to delay progression from Stage 2 to Stage 3 T1D.

The stages of type 1 diabetes (T1D) provide common ground for global efforts to prevent DKA and delay progression to disease in children and adolescents: An ISPAD consensus guideline.

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3 | EXECUTIVE SUMMARY: RECOMMENDATIONS AND PRINCIPLES

- Individuals with a first-degree relative with T1D have ~15-fold increased relative risk of developing T1D (A).
- Individuals with two or more islet autoantibodies and normoglycemia have stage 1 T1D (A).
- The vast majority (80 - 90%) of children with multiple islet autoantibodies progress to Stage 3 within 15 years, compared with ~15% who have a single islet autoantibody. Nearly 100% of children with multiple autoantibodies will ultimately progress to Stage 3 T1D (A).
- Progression rates are similar between individuals with a family history of T1D and those from the general population (A).
- Targeted screening and monitoring identifies individuals with Stage 1, Stage 2, and pre-symptomatic Stage 3 diabetes, reduces the incidence of diabetic ketoacidosis (DKA), reduces rates of hospitalization, and directs individuals toward studies seeking to delay or prevent ongoing beta cell loss (A).
- General population screening programs using combinations of genetic and autoantibody testing can identify high-risk children (A).
- Both general population and targeted screening should be coupled with education and monitoring programs for those identified with autoantibodies (B).
- Autoantibody screening at ages 2 and 6 years may provide for optimal sensitivity and positive predictive value in public health settings (B).
- When immunotherapies capable of delaying progression are approved by regulatory bodies and economic issues related to screening are optimized, general pediatric population screening for islet autoantibodies is expected to be implemented in many regions (E).
- Individuals who screen positive for genetic or immunological markers of T1D, whether identified through research or community-based screening programs, should have access to information regarding available prevention studies (E).
- An oral glucose tolerance test (OGTT) is recommended to stage disease in individuals with two or more islet autoantibodies prior to recruitment into prevention trials, and can be used to counsel individuals on risk of progression (E).
- Self-monitoring of blood glucose (SMBG), HbA1c, and continuous glucose monitoring (CGM) can be utilized to inform disease progression and may be considered where OGTT is impractical or not available (E).
- SMBG and CGM are simple measures that can be taught and provided to families allowing real-time information to prevent DKA (E).
- As screening programs expand, individuals with early and late Stage 2 and asymptomatic or symptomatic Stage 3 diabetes will be more commonly identified and additional sub-classifications or stages are likely to be adopted (e.g., Stage 3a [asymptomatic] or Stage 3b [symptomatic]) (E).

3.1 | Stages of T1D

T1D is characterized by four stages as shown in Figure 1.

Stage 1 Multiple islet autoantibodies, normal blood glucose, pre-symptomatic.

Stage 2 Multiple islet autoantibodies, abnormal glucose tolerance, usually pre-symptomatic.

Stage 3 Blood glucose above ADA diagnostic thresholds.

Stage 4 Established T1D.

A proportion of individuals who have increased genetic risk of T1D progress at variable rates to immune activation and the development of islet autoimmunity. The development of 2 or more islet autoantibodies (Stage 1), is typically followed by a period of pre-clinical dysglycemia (Stage 2), though this stage may not be detected in all individuals if progression is rapid. Individuals who develop Stage 3 T1D may be asymptomatic or symptomatic. Established T1D is described as Stage 4 T1D.

3.2 | Risk of T1D

Individuals with a first degree relative with T1D have an ~15-fold increased relative lifetime risk of T1D compared to the general population and the prevalence of T1D by age 20 years is ~5% compared to ~0.3%, respectively.[1–3] However ~85% of individuals with a new diagnosis do not have a family history of T1D.[4,5]

The various stages inform the risk of progression; children with a single islet autoantibody have a ~ 15% risk of reaching Stage 3 T1D within 10 years.[6] In contrast, children at Stage 1 have a 44% 5-year risk and 80≥90% 15-year risk of developing Stage 3 T1D, and children at Stage 2 have a 75% 5-year risk and a 100% lifetime risk of developing Stage 3 T1D.[6–9]

3.2.1 | Genetic risk

More than 70 genetic T1D variants have been identified through genome-wide association studies.[10] HLA DR and HLA DQ loci confer approximately half of the genetic risk for T1D.[11–13] The highest-risk HLA haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 (also expressed as DR3-DQ2) and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR4-DQ8). In the general population, children with the HLA DR3-DQ2/DR4-DQ8 genotype have ~5% risk for islet autoimmunity and T1D.[14–16] First-degree relatives carrying HLA DR3-DQ2/DR4-DQ8 have a further increase in risk that reaches ~20%.[15,17] Additional risk provided by non-HLA risk genes is roughly equivalent to that provided by HLA DR-DQ alone.[16] The highest non-HLA genetic contribution arises from the *INS* and *PTPN22* genes.[18] These, and other risk regions, are included in polygenic risk scores that combine HLA and non-HLA genes to substantially improve risk estimates for islet autoimmunity and T1D, particularly in the general population.[16,19,20] Notably, the risk of developing islet autoimmunity

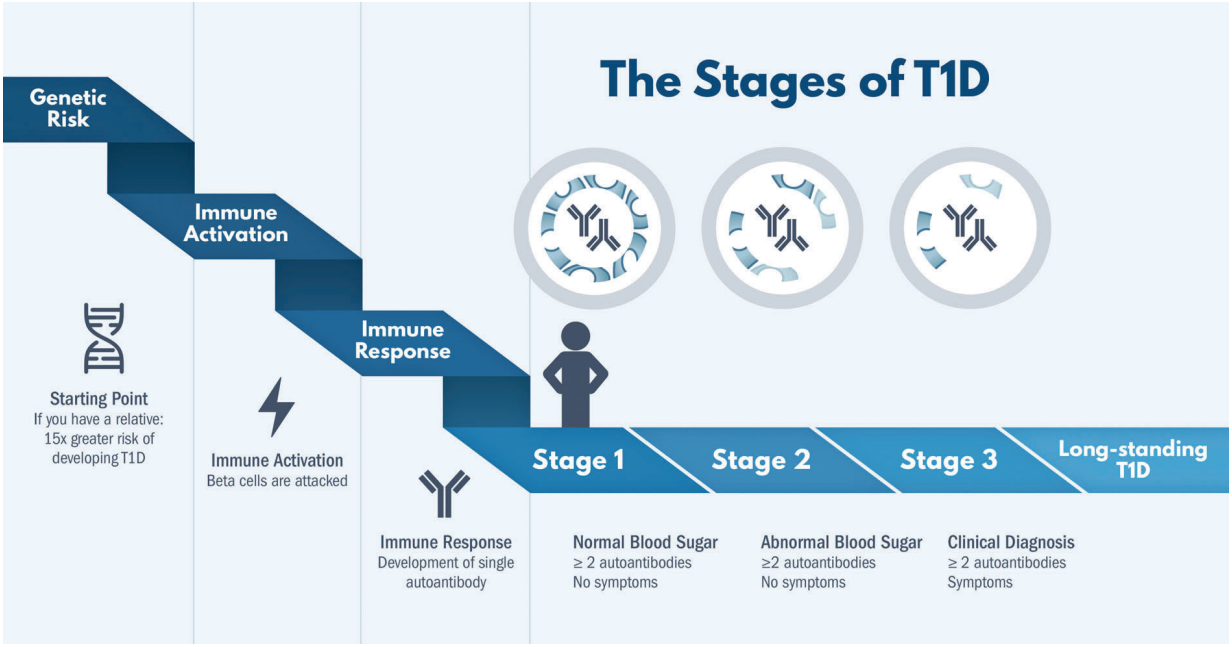

FIGURE 1 The stages of T1D (DiabetesTrialNet.org)

declines exponentially with age as does the influence of genetic factors, although there is a paucity of data in adults.[21–23] Furthermore, once a child develops multiple islet autoantibodies, HLA and polygenic risk scores have only limited further predictive value for stratifying the rate of progression to diabetes.[3,24–26]

3.2.2 | Environmental exposures

The increasing incidence of T1D globally coupled with a reduction in the proportion of individuals with the highest risk HLA haplotypes developing T1D, highlights the significant contribution environmental exposures play in the pathogenesis of T1D.[27] Different environmental exposures likely interact with multiple risk genes to drive the development of islet autoimmunity and the progression to Stage 3 T1D. Putative exposures are likely to vary across individuals and in combination with different gene—environment and environment—environment interactions. The impact of nutrition, growth, and infections and their interactions with the "omic" biological systems have been investigated in epidemiological studies and in at-risk cohorts, from birth, and more recently, from pregnancy.[28] The onset of islet autoimmunity from infancy implicates very early life exposures in some children.[28]

3.3 | Screening for pre-symptomatic T1D

Screening for risk of T1D is gaining international momentum. While the majority of screening programs remain within the context of research trials, implementation science programs in Europe, the United States, and Australia are actively demonstrating feasibility and acceptability.[29] In time, screening is likely to be embedded in local, regional, and national health systems as the standard of care. That said, optimal models for screening and staging for T1D remain unclear and will ultimately depend on several factors, including the screening objective, the structure of the local health care system, and available resources.

3.3.1 | Goals of screening

The long-term vision for T1D screening programs is to identify individuals at risk of, or with early-stage, T1D to offer them interventions to delay and, ultimately, prevent the condition. However, there are other important and currently achievable clinical benefits that drive current recommendations for screening, including to:

1. Prevent DKA and its associated short- and long-term morbidity and mortality.
2. Prepare children and families for a smoother transition to insulin therapy.
3. Advance preventative therapies through clinical trial recruitment.

Screening programs significantly reduce DKA rates, usually to less than 5%, and reduce hospitalization when coupled with long-term monitoring.[3,30–33] The rates of DKA at diagnosis range from 15% to 70% in Europe and North America and as high as 80% in under-resourced countries.[34–39] DKA prevention at diagnosis has potential lifelong benefits, including avoidance of acute morbidity (cerebral oedema, shock), neurocognitive impairment, and mortality.[40,41] There are also non-causal associations between DKA at onset and future risk of DKA,[38,42] severe hypoglycemia[42] and long-

term hyperglycemia[43–45] which increases the risk of serious future diabetes-related complications.[46] Furthermore, parental anxiety at diagnosis is approximately halved for children in screening programs compared to the general community.[3] The additional time provided for counseling, preparation for insulin therapy and education, delivered across time in the community or outpatient setting, may help reduce parental anxiety and smooth the transition to symptomatic T1D and insulin requirement.[3,47]

Screening also identifies children suitable for recruitment into clinical prevention trials, which include screening platforms such as T1D TrialNet, Type1Screen, Autoimmunity Screening for Kids (ASK), INNODIA and GPPAD (Global Platform for the Prevention of Diabetes).

3.3.2 | Target population for screening

Given the current inability to intervene effectively in the T1D disease process, international debate continues about whether screening should be population-wide or limited to first-degree family members. Notably, current evidence suggests that the rate of disease progression, once Stage 1 diabetes is confirmed, is not significantly different between individuals with a family member compared to the general population.[6,48] Routine screening for family members as part of clinical care has been proposed as an intermediate step toward general population screening.[49] However, as DKA rates are lower in individuals with a first-degree relative of T1D compared with those without[42,50] and the vast majority of individuals (at least 85%) who develop T1D do not have a family history of the disease, meaningful DKA prevention will ultimately require population-wide screening.[1,2,51]

3.3.3 | Screening modalities

There are currently two primary strategies used for T1D screening.

1. Population-wide islet autoantibody screening.
2. Genetic risk-stratified islet autoantibody screening.

Islet autoantibody screening aims to identify individuals in the target population with pre-symptomatic, Stage 1 or Stage 2 T1D. Advancements in islet autoantibody assays are enabling ultra-low blood volumes, including testing using capillary samples and dried bloodspots, which facilitate minimally invasive collection at home or in community settings.[52,53] Several groups have tried to determine optimal ages for performing autoantibody screening; modeled data from international cohort studies suggest the sensitivity of one-off autoantibody screening between the ages of 3–5 years is ~35% and can be improved to ~50% with repeated population screening at both 2–3 years and 5–7 years.[21,54] Notably, sampling from 2 years of age does not capture all children who will develop T1D and misses the small, but important, subset of infants and toddlers who rapidly develop T1D in the first 2 years of life and who have the highest rates of DKA with the greatest risk for associated morbidities.[36,37,55,56] Additional studies and analyses are needed to balance sensitivity, specificity, public health priorities, cost, and local resources when developing specific screening programs.

Genetic risk factors can be used to identify the subset of children with an increased risk of T1D who would benefit most from islet autoantibody screening. Such an approach[57,58] has also been used in GPPAD to efficiently identify children with the highest risk of developing T1D for prevention trials (e.g., in the Primary Oral Insulin Trial).[59]

Genetic risk can be broadly inferred through family history of T1D, as in T1D TrialNet, or assessed using a polygenic risk score in the general population. Some international programs, including GPPAD, evaluate polygenic risk scores from dried bloodspots collected as part of the existing Newborn Screening Program, thereby leveraging existing infrastructure and reducing the need for an additional screening intervention. As polygenic risk scores are a continuous scale, the threshold defining "at-risk" can be altered to suit the screening purpose. For example, lowering the threshold from the top 1% to the top 10% of infants by risk, reduces their risk of T1D from 10% to 2.4% but increases the number of future cases captured from ~30% to ~80%.[16,19] A high threshold may be considered more effective if the primary goal is to enroll children into prevention trials, while lower thresholds may be better suited to efforts prioritizing DKA prevention, because they capture a greater proportion of future cases.[36,38,55] Currently all polygenic risk scores for T1D have been developed using largely Caucasian datasets. While the incidence of T1D is higher in Caucasian individuals, a polygenic risk score that is either validated in or developed specifically for diverse ethnicities will be required for population-wide routine screening.[60]

3.3.4 | Follow-up in high genetic risk children

The optimal frequency of islet autoantibody testing in genetically high-risk individuals remains unclear. Clinical trials have utilized varying frequencies of antibody screening in high genetic risk children. Some efforts have screened every 3 months through 2 years of life (TEDDY), while some obtain annual antibodies, and others have proposed at least once between 1 and 5 years of age.[59,61–63] More frequent monitoring may be beneficial in infants and toddlers, given their rapid progression to Stage 3 T1D and increased risk of severe DKA. Nevertheless, the economic and psychological impacts of repeated screening must always be considered.[3,6]

3.3.5 | Glycemic surveillance in individuals with islet autoimmunity

Once a young person has multiple islet autoantibodies, they should be offered glycemic staging and ongoing monitoring to identify disease

progression. The intensity of those efforts should depend on the goals of the family or any related research study and will be influenced by resource availability. Those seeking staging for potential inclusion in a prevention trial generally require an OGTT (see next section), whereas, less intensive methods may be suitable in children who are identified or monitored outside of a research setting. Here, the goal should be to counsel families about future risk of Stage 3 T1D and the options for glycemic monitoring, how to identify signs and symptoms of hyperglycemia, preparation for a smooth transition to insulin therapy and preventing DKA.

3.3.6 | Oral glucose tolerance test

In the setting of multiple autoantibodies, the standard 2-h oral glucose tolerance test (OGTT) following 1.75 g/kg (75 g maximum) oral glucose administration remains the gold standard test for disease staging[58] (see "Stages of diabetes" section above). In addition, glucose values of ≥11.1 mmol/L (≥200 mg/dl) obtained at 30, 60, and 90 min after glucose administration have been used in the research setting to inform the risk of progression. Furthermore, mid OGTT glucose values ≥11.1 mmol/L (≥200 mg/dl) can be used to formally diagnose Stage 3 T1D in the setting of an elevated HbA1c or fasting glucose.[64,65]

Categories for fasting plasma glucose (FPG) are defined as follows:

- FPG <5.6 mmol/L (<100 mg/dl) = Stage 1 (normal fasting glucose)
- FPG 5.6–6.9 mmol/L (100–125 mg/dl) = Stage 2 (impaired fasting glucose)
- FPG ≥7.0 mmol/L (≥126 mg/dl) = Stage 3 T1D

Categories for 2-h plasma glucose following OGTT are defined as follows:

- Two-hour glucose <7.8 mmol/L (<140 mg/dl) = Stage 1 (normal glucose tolerance).
- Two-hour glucose 7.8–11.1 mmol/L (140–199 mg/dl) = Stage 2 (impaired glucose tolerance).
- Two-hour glucose ≥11.1 mmol/L (≥200 mg/dl) = Stage 3 T1D.

In the presence of multiple islet autoantibodies, the addition of other metrics such as age, sex, C-peptide, insulinoma-associated-2 autoantibody (IA–2A), HbA1c, and BMI allows calculation of scores which provide information on the risk of progression to stage 3 T1D. These include the 5-timepoint Diabetes Prevention Trial-Type 1 Risk Score (DPTRS),[66,67] the two-timepoint DPTRS60[68] and Index60[69] and the single timepoint M120.[70] These scores have similar levels of performance and are superior to using impaired glucose tolerance (IGT) alone.[68] While the majority of these scores have been developed using data from first-degree relatives being monitored in longitudinal natural history studies,[66–72] the recently published progression likelihood score from the Fr1Da program showed a 48% 2 year progression rate from stage 2 T1D to stage 3 T1D in children identified from the the general population.[73]

While the OGTT is recommended as the gold standard for staging children, especially those seeking entry into intervention trials, it is not always feasible or acceptable.[74] Alternative approaches are discussed next (Table 1).

3.3.7 | Glycosylated hemoglobin (HbA1c)

HbA1c is a specific but insensitive indicator of early onset diabetes.[77] The risk of progression is increased in the context of: (1) 10% rise in HbA1c in the non-diabetic range on two consecutive occasions collected 3–12 months apart (median time to "clinical diagnosis": 1.1 years, hazard ratio 5.7)[75]; (2) two HbA1c values >41 mmol/mol (5.9%) (median time to "clinical diagnosis": 0.9 year, hazard ratio 11.9); and (3) HbA1c >39 mmol/mol (5.7%), which is an independent predictor for progression.[3] Caution is needed in relying on HbA1c in young children who may progress rapidly, and may be missed before a rise in

TABLE 1 Monitoring tools in children with multiple islet autoantibodies

Metric	Pros	Cons	Information gained
OGTT	Gold standard Used to stage disease and predict progression	Requires glucose load and 2 to 5 blood draws over 2 h	Glycemic staging Risk scores for progression (DPTRS, DPTRS60, Index60, M120)[66–70]
Random venous glucose	One-off sample Low cost	Requires a blood draw	Similar to 2-h OGTT-derived glucose[71]
HbA1c	Highly specific Can use capillary sample	Insensitive, often normal in asymptomatic or recent onset Stage 3 diabetes, may be affected by disease states*	Risk of progression to "clinical disease": HbA1c >5.7%, or 10% rise over 3–12 months[75]
CGM	Use at home	Optimal duration and frequency of CGM wear not yet determined. Cost and access issues.	Risk of progression to "clinical disease": 10% > 7.8 mmol/L (>140 mg/dl)[76] Realtime monitoring over 24 h
Self-monitoring blood glucose	Simple use at home	Optimal timing and frequency have not been determined, unconfirmed glucose values	Immediate result

[a]See glycemic control targets and glucose monitoring chapter for further details.

HbA1c can be observed or in the setting of an undiagnosed hemoglobinopathy or other conditions that affect erythrocyte turnover.[78]

3.3.8 | Continuous glucose monitoring

Normative data taken from children, adolescents, and adults who are islet autoantibody-negative demonstrate a narrow variability in glucose using continuous glucose monitoring (CGM).[79] CGM provides real-time data and may be useful in identifying children with increased glucose variability in addition to elevated blood glucose levels.[80] In the largest pediatric study to date assessing CGM as a tool to predict progression, a cut-off of 10% time spent at >7.8 mmol/L (>140 mg/dl) had an 80% risk of progression to Stage 3 T1D over 1 year (91% specificity, 97% NPV, 88% sensitivity, 67% PPV).[76] However, further validation is needed, especially in very young children, to provide better evidence of when and how to begin insulin therapy.

3.3.9 | Random venous glucose and self-monitoring fingerstick blood glucose

In the Finnish DIPP study, the median time to diagnosis after a random plasma glucose ≥7.8 mmoL/L (140 mg/dl), was 1.0 year in children at Stage 1.[71] Random plasma glucose is a simple and low-cost measurement with comparable predictive characteristics to that of OGTT-derived 2-h glucose value, but with relatively poor sensitivity of 21% (95% CI 16%, 27%) and a specificity of 94% (95% CI 91%, 96%).[71]

Surprisingly little evidence exists for the accuracy of capillary self-monitoring fingerstick blood glucose (SMBG) in pre-symptomatic T1D in childhood, but it is a simple method that could be used in isolation or with other metrics. Adult data suggests that capillary glucose is a reliable comparator to venous glucose concentrations (85≥90% accuracy for diabetes or IGT) during the OGTT.[81,82]

3.3.10 | Recommendations for staging and monitoring

An OGTT is recommended as the gold standard for staging children for recruitment into clinical trials. When OGTT is not feasible, alternative approaches might include a 6–12 monthly HbA1c and 2-h postprandial or random glucose, dependent on risk stratification. More frequent monitoring may be offered to children at high risk of progression (e.g., those who seroconvert before age 2, with high IA–2A, or ≥3 islet autoantibodies).[3,6] If available, CGM could be added if dysglycemia is identified. HbA1c and CGM data can provide information on those progressing to insulin requirement within ~12 months, providing an opportunity to counsel individuals/carers and to commence education as an outpatient. SMBG measurements can provide families with real-time data to allow early detection of hyperglycemia and prevention of DKA.

3.4 | Psychological burden

A major concern with screening is engendering anxiety and imposing disease monitoring burden prior to insulin requirement, especially given there is currently no approved preventive therapy. The majority of children screened as being at increased genetic risk will never develop T1D[16,19] and for those with early-stage T1D, the latency period may last years.[64] "Positive" genetic and islet autoantibody screening results are associated with increased parental stress,[3,47,83,84] particularly in mothers[3,84]; however this declines rapidly within 3–12 months.[3,83] Furthermore, research programs that have monitored children both at high genetic risk and those identified through islet autoantibody surveillance programs[3] report reduced stress overall in children and their parents at the time when insulin therapy is needed compared to community controls. The Fr1da study showed that initial stress associated with multiple autoantibodies was only ~50% of that seen in families where children were diagnosed outside of the screening program.[3] These findings are likely explained by the high rates of depression and parenting stress when T1D is diagnosed and requires emergency insulin therapy.[85] The psychological burden in children and parents who continue to undergo glycemic monitoring without developing Stage 3 T1D for some years remains uncertain.

3.5 | Cost-effectiveness

A major consideration is the total cost and the incremental cost-effectiveness for screening, education, and monitoring programs. Cost-effectiveness analyses in the United States for islet autoantibody-only screening suggests that screening can be cost-effective with a 20% reduction in DKA at diagnosis and a 0.1% (1.1 mmol/mol) reduction in HbA1c during a lifetime.[86,87] Further economic modeling is required, including assessment of different screening and monitoring models of care as well as in individual countries due to differing health systems, burden of T1D, and costs of treatment locally. In the future, approval of preventive therapies will incur additional treatment costs but also likely result in substantial healthcare cost-savings and improved health benefits, further improving the incremental cost-effectiveness ratio.

In some,[88–90] but not all[91] lower resource countries, islet autoimmunity and genetic risk may be more heterogeneous, adding further complexity to screening. Lower-resourced countries often have higher rates of DKA and DKA associated-mortality, however, the lower T1D incidences in most of these countries may make screening efforts less cost-effective. Priorities in such countries continue to be correct etiological diagnosis as well as access to and improvements in clinical care for Stage 3 T1D.

3.6 | Efforts to slow disease progression

3.6.1 | Primary and secondary prevention efforts

Efforts to prevent the development of autoimmunity have historically been referred to as primary prevention, while efforts to delay

TABLE 2 Primary[59,63,95–99] and secondary[93,100–113] prevention trials in pre-T1D and intervention[94,114–133] trials in new onset T1D

Trial	Route	Intervention	Population	Primary outcome	Outcome achieved
Primary prevention					
BABYDIET	PO	Late gluten exposure	Genetically at-risk infants	Islet autoimmunity	Unsuccessful
FINDIA	PO	Bovine insulin-free formula	Genetically at-risk infants	Islet autoimmunity	**Successful**
TRIGR	PO	Hydrolyzed casein formula	Relatives, genetically at-risk infants	Stage 3	Unsuccessful
Pre-POInT	PO	Insulin	Relative, HLA risk, AAb neg, 3–7 y	AAb and T cell responses	**Successful**
Pre-POInT-early	PO	Insulin	Relative, HLA risk, AAb neg, 6 m–2 y	AAb and T cell responses	Unsuccessful[a]
POInT	PO	Insulin	Relative, HLA risk, AAb neg, 4–7 m	Islet autoimmunity	Ongoing
SINT1A	PO	*B. Infantis* probiotic	Relative, genetic risk, 7 days–6 weeks	Islet autoimmunity	Ongoing
Secondary prevention					
CORD	IV	Autologous Cord Blood	Relative or Gen Pop, Age < 15, ≥2 Ab	Stage 3	Ongoing
ENDIT	PO	Nicotinamide	Relative, ICA+, normal OGTT	Stage 3	Unsuccessful
DPT-1	IV/SC	Insulin	Relative, ICA+, IAA+, FPIR below threshold, 3–45 y	Stage 3	Unsuccessful
DPT-1	PO	Insulin	Relative, ICA+, IAA+, FPIR above threshold, 3–45 y	Stage 3	Unsuccessful[a]
DIPP	IN	Insulin	HLA risk, ≥2 AAb + 1, 1–15 y	Stage 3	Unsuccessful
INIT-I	IN	Insulin	Relative, ≥1 Ab, normal FPIR, 4–32 y	FPIR change	Unsuccessful
INIT-II	IN	Insulin	Relative, Stage 1, FPIR above threshold, 4-30y	Stage 3	Unsuccessful
Belgian registry	SC	Insulin	Relative, IA–2A+, 5–40 y	Stage 3	Unsuccessful
EPPSCIT	SC	Insulin	Relative, ≥2 AAb, 7–14 y	Stage 3	Unsuccessful
TN-07	PO	Insulin	Relative, Stage 1 (IAA+ required), 3–45 y	Stage 3	Unsuccessful[a]
Fr1da	PO	Insulin	Stage 1, 2–12 y	Immune responders then Stage 2/3	Ongoing
DiAPREV-IT	SC	GAD	Stage 1 (GADA+ required), 4–17 y	Stage 3	Unsuccessful
TN-10	IV	Teplizumab	Stage 2, 8–45 y	Stage 3	**Successful**
TN-18	IV	Abatacept	Stage 1, 6–45 y	Stage 2	Ongoing
TN-22	PO	Hydroxy-chloroquine	Stage 1, 3–45 y	Stage 2 or 3	Ongoing
Intervention					
TN-05	IV	Rituximab	Stage 3, new onset, 8–40 y	AUC C-peptide	**Successful**
AbATE	IV	Teplizumab	Stage 3, new onset, 8–30 y	AUC C-peptide	**Successful**
Protégé	IV	Teplizumab	Stage 3, new onset, 8–35 y	Insulin dose+HbA1c	Unsuccessful[a]
T1DAL	IM	Alefacept	Stage 3, new onset, 12–35 y	AUC C-peptide	Unsuccessful[a]
EXTEND	IV	Tocilizumab	Stage 3, new onset, 6–17 y	AUC C-peptide	Unsuccessful
T-Rex	IV	Autologous Tregs	Stage 3, new onset, 8–17 y	AUC C-peptide	Unsuccessful
TN-09	IV	Abatacept	Stage 3, new onset, 6–45 y	AUC C-peptide	**Successful**
START	IV	High-dose ATG	Stage 3, new onset, 12–35 y	AUC C-peptide	Unsuccessful[a]
TN-19	IV	Low-dose ATG	Stage 3, new onset, 12–45 y	AUC C-peptide	**Successful**
T1GER	SC	Golimumab	Stage 3, new onset, 6–21 y	AUC C-peptide	**Successful**
TN-14	SC	Canakinumab	Stage 3, new onset, 6–36 y	AUC C-peptide	Unsuccessful
PROTECT	IV	Teplizumab	Stage 3, new onset, 8–17 y	AUC C-peptide	Ongoing

(Continues)

TABLE 2 (Continued)

Trial	Route	Intervention	Population	Primary outcome	Outcome achieved
TN-08	SC	GAD	Stage 3, new onset, 3–45 y	AUC C-peptide	Unsuccessful
Diamyd	SC	GAD	Stage 3, new onset, 10–20 y	AUC C-peptide	Unsuccessful
DIAGNODE-3	IL	GAD	Stage 3, ≤6 m duration, 12–28 y	AUC C-peptide	Ongoing
Anti-CD40	SC	Iscalimab	Stage 3, new onset, 6–21 y	AUC C-peptide	Ongoing
BANDIT	PO	Baricitinib	Stage 3, new onset, 10–30 y	AUC C-peptide	Ongoing

Note: Stage 1 = multiple AAb-positive with normal glucose tolerance (via OGTT); Stage 2 = multiple AAb-positive with abnormal glucose tolerance; Stage 3 = clinical diagnosis of T1D. Bolded indicates emphasize those studies that have demonstrated capacity to prevent autoimmunity, delay progression of T1D or preserve beta cell function.

Abbreviations: AAb, autoantibody; FPIR, first-phase insulin response; HLA, human leukocyte antigen; IL, intra-lymphatic; IM, intramuscular; IN, intranasal; IV, intravenous; m, months; PO, per os (oral); SC, subcutaneous; y, years.

[a]Post hoc subpopulation response.

progression from Stage 1 or Stage 2 to Stage 3 diabetes are referred to as secondary prevention (Table 2). While a number of proposed therapies have been studied, teplizumab, a monoclonal antibody targeting the T cell surface marker CD3, is the only therapy that has, to date, demonstrated efficacy in delaying progression from Stage 2 to Stage 3 T1D.[92,93] This randomized, double-blind, placebo-controlled trial demonstrated Stage 3 T1D onset was delayed by a median of 2 years in first- or second-degree relatives of individuals with T1D, aged 8–50 years old, with stage 2 T1D at the time of enrolment.[92–94] Subsequent analysis demonstrated that the median delay might actually have been as long as 3 years in subjects treated with teplizumab versus placebo.[93] Teplizumab is currently being reviewed by the U.S. FDA. If granted approval, teplizumab will become the first immunotherapeutic with such a designation for individuals at risk for T1D. Trials with other drugs targeting (1) autoimmune responses; (2) antigen presentation; (3) glycemic dysregulation; and (4) beta cell stress/dysfunction are also underway.

3.6.2 | Stage 3 T1D Interventions

Stage 3 interventions or "new onset" studies seek to halt the disease, preserve residual β-cell function, and potentially delay or prevent complications of T1D in children and adults with newly diagnosed (6–12 weeks) Stage 3 T1D. Numerous efforts have been made to intervene at this relatively late stage of the disease due to the ease in identifying individuals who might still receive benefit.[134] Ultimately, relatively few agents are considered to have demonstrated capacity to delay C-peptide decline in Stage 3 disease; namely, cyclosporine, teplizumab, abatacept, alefacept, rituximab, golimumab, and low dose anti-thymocyte globulin.[94,122,126,127,135,136] However, a growing number of studies continue to focus on Stage 3. These studies not only have the prospect of providing direct benefit to newly diagnosed patients but also provide required safety data, particularly in children, where C-peptide decline is faster than in adults, to support moving therapies into Stage 1 or Stage 2 disease. Ultimately a personalized medicine approach using targeted combination therapies and timing of treatment, driven by the individual patient genetic risk and response biomarkers is likely to be the most effective means of intervening in the disease process.[136]

Clinical trials at Stage 3 of disease have historically not been available in low-income countries. These trials have also enrolled study populations that were predominantly Caucasian, in part due to study sites primarily located in the United States, Canada, United Kingdom, Europe, and Australia. So far, neither efficacy nor risks have been shown to differ by racial/ethnic background in published Stage 3 trials; however, it is possible such differences could be missed due to the preponderance of Caucasian participants. Moreover, there is emerging evidence that GRS does not differ by ethnicity.

4 | CONCLUSIONS AND RECOMMENDATIONS

Rapid expansion of screening and intervention networks, with the overall aim to prevent progression to Stage 3 diabetes and preserve beta cell function, has occurred in the last 5 years. General population screening for T1D has been propelled by technological advances in the prediction of genetic risk, low volume autoantibody assays, and advancements in trials of interventions to slow the progression of beta cell dysfunction. Screening to detect at-risk children offers the prospect of preventing DKA at presentation, and accelerated discovery of preventative interventions, through enhanced recruitment pools for clinical trials. Screening should therefore be accompanied by clinical care pathways to first reduce risk of DKA, and second, provide the young person or adult with age and stage-appropriate options to receive proven interventions or enter available intervention trials. If effective immunotherapies to delay progression and preserve beta cell function are approved by regulatory bodies, and the cost/benefit ratio related to screening is optimized, it is expected that screening will increasingly become standard practice within the general population. Primary prevention trials in infants and pre-schoolers are planned or

underway to develop immune tolerance, supplement with probiotics, or vaccinate against putative enterovirus (Coxsackie B) genotypes. Ongoing trials at Stages 1, 2, and 3 are evaluating the effects of immune-modulators acting directly and indirectly on T cells and antigen-specific therapies. It is thought that combined therapies will likely be most beneficial. The first therapeutic agent (the anti-CD3 monoclonal antibody, teplizumab) is under consideration by regulatory bodies to delay progression from Stage 2 to 3 T1D. Increasingly therapies will become more individualized to target different mechanisms in the disease pathway, analogous to treatments for other autoimmune diseases such as lupus erythematosus and rheumatoid arthritis.

AUTHOR CONTRIBUTIONS

REJB and KJB were co-first authors and reviewed the literature, drafted sections of the guidelines, oversaw completion of the first draft of the guidelines, and edited the manuscript. JJC, AGZ, DKW, MK, CS, KC, KAD, and JL reviewed the literature, provided drafts of sections and edited the manuscript. MEC was the lead of the ISPAD guidelines editorial committee, edited the manuscript, and served as co-senior author. MJH outlined the guidelines, reviewed the literature, drafted sections of the guidelines, edited the manusript, and served as the corresponding senior author. The authors gratefully acknowledge the editorial assistance of Dr. Leena Priyambada.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13410.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Besser REJ, Bell KJ, Couper JJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Stages of type 1 diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1175-1187. doi:10.1111/pedi.13410

Received: 29 September 2022 | Accepted: 30 September 2022

DOI: 10.1111/pedi.13426

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents

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KEYWORDS: diabetes mellitus classification, genetics, MODY, monogenic, neonatal diabetes

1 | WHAT IS NEW OR DIFFERENT

- Addition of recently described subtypes of monogenic diabetes, including causes associated with diabetes in infancy (*CNOT1*, *ONECUT1*, *YIPF5*, *EIF2B1*, *KCNMA1*); and genetic causes associated with diabetes later in life (*TRMT10A*, *DNAJC3*, *KCNK16*, *DUT*).
- The expanding list of genes causing monogenic diabetes further emphasizes comprehensive next-generation sequencing (NGS) as the best approach to allow for early molecular diagnosis that can guide treatment, rather than phenotype-based targeted testing, particularly for neonatal diabetes (NDM).
- Use of increasingly available publicly accessible information about specific variants to allow for the appropriate classification of pathogenicity of gene variants according to guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP), bolstered by the establishment of international Monogenic Diabetes Expert Panels for gene curation and variant curation with the

TABLE 1 Monogenic subtypes of neonatal and infancy-onset diabetes

Gene	Locus	Inheritance	Other clinical features	Reference
Abnormal pancreatic development:				
PLAGL1/HYMAI	6q24	Variable *(imprinting)*	TNDM ± macroglossia ± umbilical hernia	20
ZFP57	6p22.1	Recessive	TNDM (multiple hypomethylation syndrome) ± macroglossia ± developmental delay ± umbilical defects ± congenital heart disease	29
PDX1	13q12.1	Recessive	PNDM + pancreatic agenesis (steatorrhea)	264
PTF1A	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	265
PTF1A enhancer	10p12.2	Recessive	PNDM + pancreatic agenesis without CNS features	133
HNF1B	17q21.3	Dominant	TNDM + pancreatic hypoplasia and renal cysts	23
RFX6	6q22.1	Recessive	PNDM + intestinal atresia + gall bladder agenesis	266,267
GATA6	18q11.1-q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	134
GATA4	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	268
GLIS3	9p24.3-p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	269
NEUROG3	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	270
NEUROD1	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	271
PAX6	11p13	Recessive	PNDM + microphthalmia + brain malformations	272
MNX1	7q36.3	Recessive	PNDM + developmental delay + sacral agenesis + imperforate anus	4
NKX2-2	20p11.22	Recessive	PNDM + developmental delay + hypotonia + short stature + deafness + constipation	273
CNOT1	16q21	Spontaneous	PNDM + pancreatic agenesis + holoprosencephaly	274
ONECUT1	15q21.3	Recessive	PNDM + pancreatic hypoplasia + gall bladder hypoplasia	275
Abnormal β-cell function:				
KCNJ11	11p15.1	Spontaneous or dominant	PNDM/ TNDM ± DEND	41
ABCC8	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM ± DEND	42
INS	11p15.5	Recessive	Isolated PNDM or TNDM	24
GCK	7p15-p13	Recessive	Isolated PNDM	107
SLC2A2 (GLUT2)	3q26.1-q26.3	Recessive	Fanconi-Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	276
SLC19A2	1q23.3	Recessive	Roger's syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	277
KCNMA1	10q22.3	Spontaneous	PNDM (not all cases) + developmental delay + intestinal malformations + cardiac malformations + bone dysplasia + dysmorphic features	278
Destruction of β cells:				
INS	11p15.5	Spontaneous or dominant	Isolated PNDM	90
EIF2AK3	2p11.2	Recessive	Wolcott-Rallison syndrome: PNDM + skeletal dysplasia + recurrent liver dysfunction	98
IER3IP1	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	279
FOXP3	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, elevated IgE)	280
WFS1	4p16.1	Recessive	PNDM[a] + optic atrophy ± diabetes insipidus ± deafness	189
WFS1	4p16.1	Dominant	PNDM or infancy-onset diabetes + congenital cataracts + deafness	281
EIF2B1	12q24.31	Spontaneous	PNDM + episodic hepatic dysfunction	282
YIPF5	5q31.3	Recessive	PNDM + severe microcephaly + epilepsy	283

(Continues)

TABLE 1 (Continued)

Gene	Locus	Inheritance	Other clinical features	Reference
STAT3	17q21.2	Spontaneous	PNPM + enteropathy + other autoimmunity such as cytopenias	116
CTLA4	2q33.2	Spontaneous	Lymphoproliferative syndrome + enteropathy + cytopenias + diabetes + thyroiditis	127
ITCH	20q11.22	Recessive	PNDM + facial dysmorphism + multi-system autoimmunity	128
IL2RA	10p15.1	Recessive	Lymphoproliferation + multi-system autoimmunity + diabetes	129
LRBA	4q31.3	Recessive	PNDM + enteropathy + hypothyroidism + autoimmune hemolytic anemia	118

[a]The mean age of diagnosis among persons with *WFS1* mutations is approximately 5 years.[194]
Source: modified from Reference 47.

TABLE 2 Most important subtypes of MODY and associated clinical features

Gene	Locus	Clinical features	Treatment	References
GCK	7p15-p13	Mild asymptomatic hyperglycemia	None	284
HNF1A	12q24.2	Renal glucosuria	Sulphonylurea	285
HNF4A	20q12-q13.1	Macrosomia and neonatal hypoglycaemia, renal Fanconi syndrome (mutation specific)	Sulphonylurea	286
HNF1B	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	287
KCNJ11	11p15	Proband or relatives may have history of TNDM and/or neuropsychological difficulties	High-dose sulphonylurea	
ABCC8	11p15	Proband or relatives may have history of TNDM and/or neuropsychological difficulties	High-dose sulphonylurea	

elaboration of gene-specific rules (https://clinicalgenome.org/affiliation/50016).

- Further understanding of the neuroendocrine aspects of ATP-sensitive potassium channel (KATP) related NDM (KATP-NDM) is now included.
- Clarification that a small fraction of NDM is likely to be autoimmune type 1 diabetes (T1D) and autoimmune etiology distinct from T1D occurring in Trisomy 21.
- Among young persons with diabetes with a clinical diagnosis of type 2 diabetes (T2D), a low but significant fraction can be found to carry pathogenic MODY mutations; highlighting the importance of considering a monogenic cause even when obesity may be present.
- The rate of diabetes-related complications may be lower in HNF1A diabetes who have been treated with sulfonylureas (SU).
- Liver (with or without pancreas) transplantation can improve the outcomes of individuals with Wolcott-Rallison syndrome.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | General aspects of monogenic diabetes

- Monogenic diabetes is uncommon, but accounts for ~2.5%–6.5% of pediatric diabetes **B**.
- NGS enables the simultaneous analysis of multiple genes at a lower cost per gene providing comprehensive testing **B**.
- NGS is the recommended methodology for study of suspected monogenic diabetes, unless a very specific and highly suggestive clinical scenario is present, such as glucokinase (*GCK*) mutations, which cause a distinct phenotype of asymptomatic and stable mild fasting hyperglycemia **B**.
- Results of genetic testing should be reported and presented to families in a clear and unambiguous manner **E**.
- Referral to a specialist in monogenic diabetes or an interested clinical genetics unit is suggested to guide specific management considerations and/or facilitate genetic testing of other related affected or pre-symptomatic individuals **E**.

2.2 | Neonatal diabetes

- All infants diagnosed with diabetes in the first 6 months of life are recommended to have immediate molecular genetic testing **B**.
- Genetic testing maybe be considered in infants diagnosed between 6 and 12 months, especially in those without islet autoantibodies or who have other features suggestive of a monogenic cause **C**.
- A molecular genetic diagnosis of NDM provides essential information regarding treatment options, associated features, and diabetes course that may have a significant clinical benefit **B**.

TABLE 3 Classification of Syndromes of severe insulin resistance

IR syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signaling defects	Receptor defect	*INSR* (AR or AD)	Decreased	Normal or elevated	No dyslipidemia or hepatic stetosis
	Post receptor defects	*AKT2*, *TBC1D4* (AD)			Elevated fasting triglycerides and LDL-cholesterol, hepatic steatosis, diabetes (*AKT2*)
Adipose tissue abnormalities	Monogenic obesity	*MC4R* (AD) *LEP*, *LEPR*, *POMC* (AR) Others	Increased (low in *LEP*)		Tall stature (*MC4R*) Hypogonadism (*LEP*) Hypoadrenalism (*POMC*)
	Congenital generalized lipodystrophy	*AGPAT2*, *BSCL2* (AR) Others	Decreased	Decreased	Severe dyslipidemia (high triglycerides, low HDL- cholesterol) Hepatic stetosis
	Partial lipodystrophy	*LMNA*, *PPARG*, *PIK3R1* (AD) Others	Variable		Myopathy and cardiomyopathy (*LMNA*) Pseudo-acromegaly (*PPARG*) SHORT syndrome with partial lipodystrophy, and diabetes (PIK3R1)
Complex syndromes	Alström	*ALMS1* (AR)			Cone-rod dystrophy leading to blindness, sensorineural hearing loss, diabetes and cardiomyopathy
	Bardet-Biedl	*BBS1 to BBS18* (mostly AR)			Cone-rod dystrophy, obesity, renal dysfunction, polydactyly, learning disabilities, hypogonadism and diabetes
	DNA damage repair disorders	*WRN* (AR) *BLM* (AR)			Scleroderma-like skin changes, cataracts, increased cancer risk, atherosclerosis and diabetes; Sun-sensitive, telangiectatic skin changes; increased cancer risk and diabetes
	Primordial dwarfism	*PCNT* (AR)			Microcephalic osteodysplastic primordial dwarfism and diabetes

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.
Source: modified from Parker et al. Reference 228.

- Treatment with SU, especially glibenclamide (also known as glyburide), is recommended for NDM due to *KCNJ11* and *ABCC8* abnormalities **B**.
- Glibenclamide significantly improved neurological and neuropsychological abnormalities in individuals with neonatal onset diabetes due to *KCNJ11* or *ABCC8* mutations. Earlier treatment initiation was associated with greater benefits **B**.

2.3 | Maturity onset diabetes of the young

- The diagnosis of maturity onset diabetes of the young (MODY) is recommended in the following scenarios:
  - A family history of diabetes in a parent and first-degree relatives of that affected parent in persons with diabetes who lack the characteristics of T1D and T2D **B**.
- Testing for GCK-MODY, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population, is recommended for mild stable fasting hyperglycemia that does not progress **B**.
- In familial autosomal dominant symptomatic diabetes, mutations in the *HNF1A* gene (HNF1A-MODY) should be considered as the first diagnostic possibility **B**.
- Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (HNF1B-MODY), macrosomia and/or neonatal hypoglycemia (HNF4A-MODY), exocrine pancreatic dysfunction or pancreatic cysts (CEL-MODY), or hearing impairment and maternal inheritance of diabetes (mitochondrial diabetes) **C**.
- Obesity alone should not preclude genetic testing in young persons, especially if: **C**
  - family history is strongly suggestive of autosomal dominant inheritance of diabetes
  - if some affected family members are NOT obese
  - and/or, there are no other features of metabolic syndrome.
- Some forms of MODY are sensitive to SU, such as HNF1A-MODY and HNF4A-MODY **B**
- Mild fasting hyperglycemia due to GCK-MODY is not progressive during childhood. These persons do not develop complications **B**

and do not respond to low dose insulin or oral agents **C**. They should not receive treatment.

- Establishing the correct molecular diagnosis of MODY is suggested for the following reasons: **C**
  - avoids misdiagnosis as T1D or T2D
  - may offer more accurate prognosis of risk of complications
  - may avoid stigma and limitation of employment opportunity (especially in the case of GCK-MODY)
  - may enable prediction of risk in relatives, including offspring
  - can be cost-effective when appropriately selected individuals are screened

3 | INTRODUCTION

Monogenic diabetes results from one or more defects in a single gene or chromosomal *locus*. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a de novo mutation.

Monogenic diabetes has been categorized as neonatal or early infancy diabetes (Table 1), MODY (Table 2), diabetes associated with extra-pancreatic features, and monogenic insulin resistance (IR) syndromes (Table 3).

4 | CLINICAL RELEVANCE OF DIAGNOSING MONOGENIC DIABETES

- Identification of children with monogenic diabetes usually improves their clinical care.[1]
- Making a specific molecular diagnosis helps predict the expected clinical course of the disease and guides the most appropriate management, including pharmacological treatment, in a particular person with diabetes.
- Characterizing the specific molecular diagnosis has important implications for the family as it informs genetic counseling. It also frequently triggers extended genetic testing in other family members with diabetes or hyperglycemia who may also carry a causal mutation, thereby improving the classification of diabetes.[2,3]

5 | SELECTING CANDIDATES FOR MOLECULAR TESTING

In contrast to T1D and T2D, where there is no single definitive diagnostic test, molecular genetic testing is both sensitive and specific for diagnosing monogenic diabetes. Appropriate informed consent/assent must be prospectively obtained from the affected person and/or legal guardians and should be strongly considered in persons with a suspected monogenic cause. Genetic testing is currently available (and may be free of charge on a research basis in certain academic institutions) in many countries around the world: https://www.diabetesgenes.org; http://monogenicdiabetes.uchicago.edu; www.mody.no; http://euro-wabb.org; https://www.ospedalebambinogesu.it/test-genetici-89757/; https://robertdebre.aphp.fr/equipes-cliniques/pole-biologie/genetique/genetique-moleculaire/#1461944418-1-40 and several commercial laboratories.

NGS enables the simultaneous analysis of multiple genes at a lower cost per gene and has mostly replaced single gene testing by Sanger sequencing or other methods.[4–8] Such NGS panels provide an efficient means of comprehensive testing that results in earlier genetic diagnosis, which in turn facilitates appropriate management as well as monitoring for other associated features before they become clinically apparent. It is important to note that NGS testing panels are still expensive, so it remains appropriate to use a judicious approach to selecting persons with diabetes for comprehensive molecular testing and in specific circumstances (such as living in a resource-poor setting), Sanger sequencing of a limited number of the most treatment-relevant genes may be the most practical approach. Moreover, some NGS panels have included genes lacking robust evidence for a causal role in monogenic diabetes and this can result in misdiagnosis and confusion for the person with diabetes and other affected family members; however, increasing international collaboration between testing laboratories has begun to limit such examples of inaccurately reported genetic testing results. Sanger sequencing remains appropriate as an efficient cost-effective method for testing of a variant found by NGS testing of the first individual in other affected or at-risk family members (cascade testing).

In NDM, genetic testing may be cost saving because of improved cheaper treatment; testing for MODY in appropriate populations can also be cost-effective.[2,3,9] Targeted gene sequencing, however, may still be appropriate for some persons with diabetes; for example, a pregnant female with mild fasting hyperglycemia, in whom a rapid test to identify a *GCK* mutation will inform management of the pregnancy. For most people with diabetes suspected to have a monogenic cause, NGS provides an optimal approach for clinical care as it provides a genetic diagnosis that often precedes the development of additional clinical features, informs prognosis, and guides clinical management.[2,3,9]

6 | WHEN TO SUSPECT A DIAGNOSIS OF T1D IN CHILDREN MAY NOT BE CORRECT?

Features that suggest monogenic diabetes in children initially thought to have T1D are listed below. Except for the age of diagnosis less than 6 months, none of these are pathognomonic and should be considered together rather than in isolation:

1. Diabetes presenting before 6 months of age (as T1D is extremely rare in this age group), or consider NDM if the diagnosis is between 6 and 12 months and there is no evidence of autoimmunity or if the person with diabetes has other features such as congenital defects, or an unusual family history.[10,11]
2. Family history of diabetes in one parent and other first-degree relatives of that affected parent.
3. Absence of islet autoantibodies, especially if checked at diagnosis.
4. Preserved β-cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (at least 5 years after diagnosis).

7 | WHEN TO SUSPECT A DIAGNOSIS OF T2D IN CHILDREN MAY NOT BE CORRECT

In young people, T2D often presents around puberty and the majority are obese. As there is no diagnostic test for T2D and because obesity has become so common in children, children and adolescents with monogenic diabetes may also be obese and can be very difficult to distinguish from T2D.[1] One recent study found that 3% of obese youth with presumed T2D in fact carried pathogenic monogenic diabetes variants.[5] Features that suggest monogenic diabetes in young people with suspected T2D are listed below:

1. Lack of consistent severe obesity among affected family members.
2. Lack of consistent acanthosis nigricans and/or other markers of metabolic syndrome (hypertension, low HDL-cholesterol, etc.) among affected family members.
3. Family history of diabetes in one parent and other first-degree relatives of that affected parent, especially if any affected family member lacks obesity and other markers of metabolic syndrome.
4. Unusual distribution of fat, such as central fat with thin or muscular extremities.

8 | INTERPRETATION OF GENETIC FINDINGS

Despite the obvious clinical benefits derived from genetic diagnostic services:

- Care needs to be exercised in the interpretation of genetic findings. The way the clinician interprets the genetic report will have a major effect on the future clinical management of the person with diabetes and his/her family.
- Results should be presented in a clear and unambiguous way to ensure that both clinicians and the person with diabetes and their families receive adequate and understandable information. Specific recommendations describing the information that should be included in the molecular genetics laboratory report for MODY testing have been published.[12]
- This includes the method used for mutation screening, limitations of the test, classification of the variant as pathogenic/likely pathogenic or of uncertain significance (with supporting evidence included where appropriate), and information about the likelihood of the disease being inherited by the offspring.
- The laboratory reporting the results should adhere to the ACMG/AMP variant classification guidelines.[13] Many genetic testing laboratories have been participating in the Monogenic Diabetes Variant Curation Expert Panel (https://clinicalgenome.org/affiliation/50016/) that has provided more definitive curation of hundreds of variants that are freely accessible and recognized by the US FDA. This resource can be utilized to check whether a variant in question has been deemed "pathogenic" or "likely pathogenic" in which case there should be confidence that this is the cause of diabetes, or if "benign" or "likely benign" that another cause should be considered. Whether or not the testing report follows ACMG/AMP guidelines, when testing reveals a variant of uncertain significance (VUS), or when predictive testing of asymptomatic individuals is requested, consultation with an expert center with experience in monogenic diabetes can often provide additional insight on the interpretation and recommendations of how to proceed.

9 | SPECIFIC SUBTYPES OF MONOGENIC DIABETES AND THEIR MANAGEMENT

In children, the majority of cases of monogenic diabetes result from mutations in genes causing β-cell loss or dysfunction, although diabetes can rarely occur from mutations resulting in very severe IR. From a clinical perspective, specific scenarios when a diagnosis of monogenic diabetes should be considered include:

1. Diabetes presenting before 6 months of age, which is known as NDM.
2. Autosomal dominant familial mild hyperglycemia or diabetes.
3. Diabetes associated with extra-pancreatic features (such as, for example, congenital heart or gastrointestinal defects, brain malformations, severe diarrhea, or other autoimmune conditions in a very young child).
4. Monogenic IR syndromes (see below: characterized by high insulin levels or high insulin requirements; abnormal distribution of fat with a lack of subcutaneous fat, especially in extremities; dyslipidemia, especially high triglycerides; and/or significant acanthosis nigricans).

9.1 | Neonatal diabetes diagnosed within the first 6–12 months of life

- All infants diagnosed under 6 months should have genetic testing for a monogenic cause, regardless of islet autoantibody status.
- The clinical presentation of autoimmune T1D may rarely occur before age 6 months[11,14]; a recent study suggested approximately 4% of cases may be T1D (see section of autoimmune monogenic diabetes).[15]
- One recent study observed trisomy 21 in a much greater than expected fraction of NDM individuals, with the conclusion that trisomy 21 can cause an autoimmune form of diabetes that appears to be distinct from the more common autoimmune T1D.[16]
- Some cases of NDM can be diagnosed between 6–12 months[17,18] although the vast majority of these older infants with diabetes have T1D. Reasons to consider genetic testing in those diagnosed between 6–12 months include: negative autoantibody testing, extra-pancreatic features such as gastrointestinal anomalies or congenital defects, unusual family history, or even the development of multiple autoimmune disorders at a young age.
- Approximately half will require lifelong treatment to control hyperglycemia and are denominated as PNDM.
- In the remaining cases, known as transient neonatal diabetes (TNDM), diabetes will remit within a few weeks or months although it might relapse later in life.

- PNDM and TNDM present more frequently isolated or is the first feature to be noted.
- Some infants with diabetes show a variety of associated extra-pancreatic clinical features that may point to a particular gene; however, because these features often are not apparent initially, they will not always be helpful in guiding genetic testing and instead, early comprehensive testing will often allow for the genetic testing result to precede the recognition of other features (Table 1).

Many infants with NDM are born small for gestational age, which reflects a prenatal deficiency of insulin secretion as insulin exerts potent growth-promoting effects during intrauterine development.[19]

9.2 | Transient neonatal diabetes from imprinting anomalies on 6q24

- The genetic basis of TNDM has been mostly uncovered: approximately two-thirds of cases are caused by abnormalities in an imprinted region on chromosome 6q24.[20,21]
- Activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K_{ATP}) channel of the β-cell membrane (*KCNJ11* or *ABCC8*) cause the majority of the remaining cases (KATP-NDM).[22]
- A minority of cases of TNDM is caused by mutations in other genes, including *HNF1B*,[23] *INS*[24] among others.

Anomalies at the 6q24 locus, spanning two candidate genes *PLAGL1* and *HYMAI*, are the single most common cause of NDM and always result in TNDM.[25] In normal circumstances, this region is maternally imprinted so that only the allele inherited from the father is expressed. TNDM is ultimately associated with overexpression of the imprinted genes.[26] To date, three different molecular mechanisms have been identified: (1) paternal uniparental disomy of chromosome 6 (UPD6) either complete or partial; this accounts for 50% of sporadic TNDM cases, (2) unbalanced paternal duplication of 6q24 (found in most familial cases), and (3) hypomethylation of the maternal allele (found in sporadic cases).[27] Methylation defects may result from an isolated imprinting variant affecting only the 6q24 locus or may arise in the context of a generalized hypomethylation syndrome caused by multiple imprinting alterations across the genome, that is, multi-locus imprinting disturbance (MLIDs) along with other clinical features including congenital heart defects, brain malformations, and so forth.[28] Some cases of TNDM secondary to multiple methylation defects are caused by recessively acting mutations in *ZFP57*, a gene on chromosome 6p involved in the regulation of DNA methylation.[29]

Neonates with diabetes caused by 6q24 abnormalities are born with severe intrauterine growth retardation (IUGR) and one-third of them show macroglossia; more rarely, an umbilical hernia is present. They develop severe but nonketotic hyperglycemia very early, usually during the first week of life.[27,30]

- Despite the severity of the initial presentation, the insulin dose can be tapered quickly so that most infants do not require any treatment by a median age of 12–14 weeks and the rate of remission is close to 100%.[31]
- Because most cases exhibit some degree of endogenous β-cell function, insulin therapy is not always necessary, and these infants may respond to oral SU or other drugs used for T2D.[31–34]
- In some, a transition to remission has been observed with no need for insulin therapy or initial SU treatment.[34]
- Some cases with TNDM have shown a positive response to SU.[34,35]
- Following remission, a low proportion of affected infants and children will exhibit clinically significant hypoglycemia that in some cases requires long-term treatment.[36,37] During remission, transient hyperglycemia may occur during intercurrent illnesses.[38]
- Over time, diabetes relapses in at least 50%–60% of these young people; in one large cohort followed until 18 years of age, relapse occurred in 85%.[39] Relapse usually occurs around puberty, although recurrences have been reported as young as 4 years of age.

Therefore, parents of children with TNDM should internalize the high risk of their child's future diabetes relapse and these children may benefit from annual HbA1c testing. Relapse clinically resembles early-onset T2D and is characterized by a loss of the first-phase insulin secretion.[34] Long-term metabolic and socio-educational follow-up has shown that these persons have decreased educational attainment, and those with diabetes have lower insulin secretion capacity.[40]

The phases described above do not present uniformly in every affected child. Interestingly, some carrier relatives develop T2D or gestational diabetes in adulthood without any evidence of having had NDM, as well as in a small fraction of people with early-onset, non-obese, non-autoimmune diabetes without a history of NDM. This suggests significant variability in phenotype, possibly related to other genetic or epigenetic factors that may influence the clinical expression of alterations of chromosome 6q24.[20,31]

The role of genetic counseling depends on the underlying molecular mechanism. Uniparental disomy of chromosome 6 is generally sporadic and, therefore, the risk of recurrence in siblings and offspring is low. When paternal duplication of the 6q24 region is found, affected newborn males have a 50% chance as adults of transmitting the mutation and the disease to their children. In contrast, newborn affected females will as adults pass on the duplication, but their children will not develop the disease. In this case, TNDM may recur in the next generation as their asymptomatic sons pass on the molecular defect to their own children. Some methylation defects (i.e., *ZFP57* mutations) show an autosomal recessive inheritance and hence the recurrence risk is 25% for siblings and almost negligible for the offspring of an affected individual.

9.3 | Permanent neonatal diabetes due to mutations in the K_{ATP} channel genes (KATP-NDM)

KATP-NDM is the commonest cause of PNDM[41–45] and the second most common cause of TNDM.[22] The prevalence of KATP-NDM in a

specific group depends on the degree of consanguinity. In outbred populations the commonest known cause of PNDM are abnormalities in the K_{ATP} channel or *INS* genes.[9,46] If parents are related, Wolcott-Rallison syndrome or homozygous mutations in the *GCK* gene are the most common etiologies.[47] The causes of up to 20% of PNDM cases remain unknown.

- K_{ATP} channels are hetero-octameric complexes formed by four pore-forming Kir6.2 subunits and four SUR1 regulatory subunits, encoded by the genes *KCNJ11* and *ABCC8*, respectively.[48] They regulate insulin secretion by linking the intracellular metabolic state to the β-cell membrane electrical activity. Any increase in the intracellular metabolic activity induces a rise in the ATP/ADP ratio within the pancreatic β-cell. The high ATP/ADP ratio closes the K_{ATP} channels and leads to cell membrane depolarization which ultimately triggers insulin secretion.[49]
- Activating mutations in *KCNJ11* or *ABCC8*, prevent K_{ATP} channel closure and hence reduce insulin secretion in response to hyperglycemia, resulting in diabetes[4241,43,45] (Figure 1). A loss-of-function nonsense mutation in *ABCC8*, resulting in gain-of-channel function, has also been reported.[50]

Approximately 90% of persons with *KCNJ11* mutations have PNDM while ~10% develop TNDM, whereas *ABCC8* mutations more frequently (~66%) cause TNDM.[42,51] There are no significant differences in the severity of IUGR or the age at diagnosis of diabetes between the two subtypes of NDM.[22] K_{ATP} channel mutations typically show milder IUGR and are diagnosed slightly later than infants with 6q24 abnormalities, indicating a less severe insulin deficiency during the last months of intrauterine development and at the time birth. In K_{ATP}-TNDM, diabetes usually remits later and relapses earlier than in 6q24-TNDM.[22] The low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis in KATP-NDM suggest insulin dependency.[52]

In addition to diabetes, about 20% of affected children with *KCNJ11* mutations present with associated neurological features[41,53,54] in keeping with the expression of K_{ATP} channels in neurons and muscle cells.[49,55] The most severely damaging mutations are also associated with marked developmental delay and early-onset epilepsy, known as DEND (developmental delay, epilepsy, and NDM) syndrome. An intermediate DEND syndrome characterized by NDM and less severe developmental delay without epilepsy is more common. Recent studies utilizing detailed testing have revealed that mild neurodevelopmental abnormalities occur even in those with milder mutations previously thought to cause only isolated diabetes. In some studies using sibling controls, mild but significant impairments were found in several domains, including IQ, measures of academic achievement, and executive function. Many of these children met criteria for developmental coordination disorder (particularly visual–spatial dyspraxia), attention deficit hyperactivity disorder, anxiety disorder, or autism, and/or had behavioral or sleep difficulties.[39,56–58]

- Approximately 90% of children with activating mutations in the KATP channel genes can be switched from insulin to off-label SU tablets.[59–61] A suspension of glibenclamide has shown to be safe and effective in individuals with NDM,[62] and received authorization for use in the European Union.[63]
- Treatment with SU dramatically improves glycemic management, which appears to be durable long-term with only minimal mild hypoglycemia.[64,65]

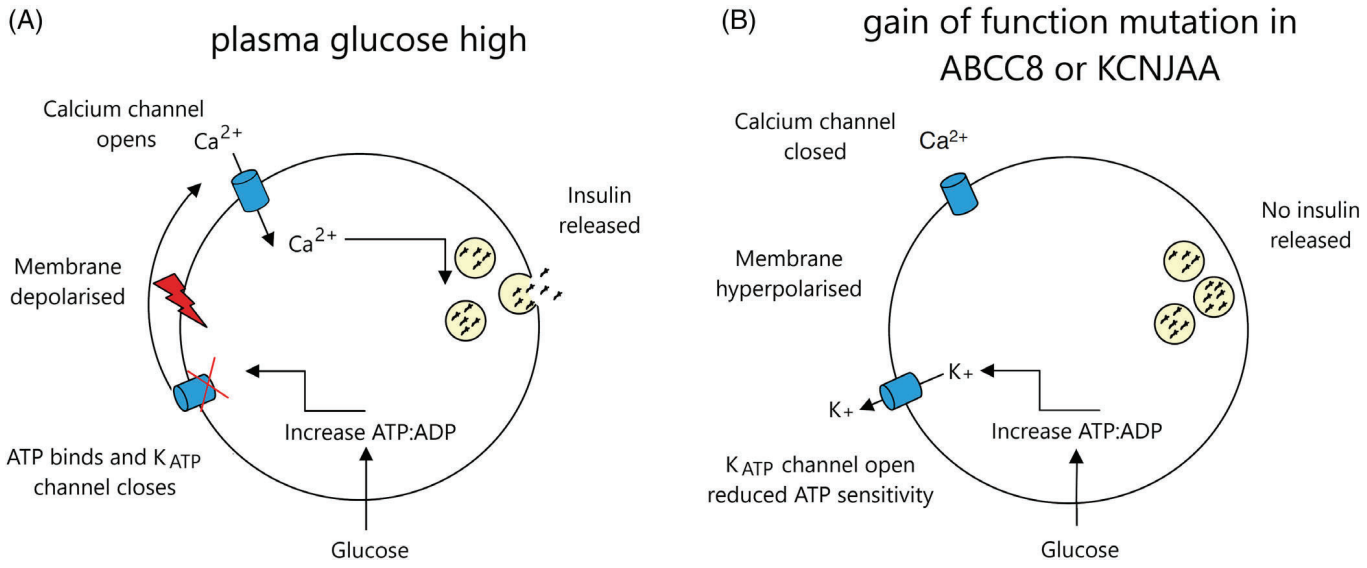

FIGURE 1 Insulin secretion from the pancreatic beta cell in (A) normal cell in a high plasma glucose environment and (B) in a cell with a K-ATP channel mutation. *Source*: adapted from Reference 263. (A) Glucose enters the cell and is metabolized, causing an increase in ATP, K-ATP channel closure is induced via ATP binding, the membrane is depolarized, and calcium influx is triggered resulting in the release of insulin from its storage vesicles. (B) A gain of function mutation in the K-ATP channel results in the failure of ATP to bind to the channel, causing the channel to remain open, the membrane stays hyperpolarized and no insulin is released

- The glibenclamide doses required when calculated based on body weight are higher compared to the dose used in adults with T2D, typically needing around 0.5 mg/kg/day, although doses as high as 2.3 mg/kg/day have been occasionally reported.[66–68] The dose required depends mostly on the age at which the person starts SU, as well as the specific mutation.[69,70]
- Many persons have been able to progressively reduce the dose after transition while maintaining excellent glycemic management.[71,72] The only side effects reported to date are transient diarrhea and staining of the teeth.[73,74] Recently, it has been reported that celiac disease my cause secondary SU failure not explained by lack of adherence to therapy.[75]
- Insulin secretion in children with diabetes treated with adequate SU doses seems to be driven mostly by food intake via non-KATP dependent pathways. Meals composed of either all carbohydrate or only protein/fat resulted in similar insulin responses, highlighting the importance of carbohydrate intake with most meals to avoid post-prandial hypoglycemia.[76]
- Some studies have shown that SU may penetrate the blood–brain barrier, but maintenance of cerebrospinal fluid levels may limit the benefit of SU on neurodevelopmental outcome, and use of other agents could be considered.[77–79]
- Although SU appears to partially improve some of the neurological symptoms, the degree of improvement likely also depends on how early treatment is started.[80–83]
- Neurological features have been reported less frequently in persons with *ABCC8* mutations, who more often have TNDM.[42,43] However, those with PNDM due to *ABCC8* mutations had a similar range of difficulties as those with PNDM due to *KCNJ11* mutations.[84]
- The *ABCC8* encoded SUR-1 protein is crucial in retinal function and SU (glibenclamide) confers direct retinal neuroprotection through SUR-1 mediated mechanisms.[85,86]
- A recent study utilized patient-derived iPSCs to generate cerebral organoids and found major defects in early development of cortical neuronal network in V59M mutants compared to controls, that could partially be rescued by the SU tolbutamide.[87]

Activating mutations in *KCNJ11* causing NDM are always heterozygous. Since about 90% of these mutations arise de novo, there is usually no family history of NDM[88] but familial cases show an autosomal dominant pattern of inheritance. Recurrence risk for the offspring of an affected person is 50%. This is also true for most people with activating mutations in *ABCC8*. However, some persons are homozygous or compound heterozygous for two different mutations and NDM is recessively inherited.[43] In this case, the risk of NDM for future siblings is 25%, but almost non-existent for the offspring of the affected person unless the other parent is also a carrier for the same mutation. Germline mosaicism (mutations present in the gonads but not detectable in blood) has been reported in several families[88] and hence unaffected parents of a child with an apparently de novo mutation should be advised that the recurrence risk in siblings is low but not negligible.

9.3.1 | Neonatal diabetes due to mutations in INS gene

Mutations in the proinsulin gene (*INS*) are the second most common cause of PNDM after KATP channel mutations.[46,89–92] Individuals with diabetes due to *INS* mutations lack any extra-pancreatic features and are insulin dependent.[89,91,93] Dominant heterozygous mutations are most common and usually result in a misfolded proinsulin molecule that is trapped and accumulates in sub-cellular compartments, leading to endoplasmic reticulum stress and ß-cell apoptosis.[93–95] Recessive biallelic (homozygous or compound heterozygous) mutations lead to loss or inactivation of proinsulin.[24] These mutations do not cause slowly progressive β-cell destruction but result in a lack of insulin biosynthesis before and after birth, which explains much lower birth weights and earlier presentation of diabetes in affected children. Since the disease is recessively inherited, there will be a 25% recurrence risk in siblings when each parent has been confirmed to be a carrier of a causal *INS* variant.

The severity of IUGR in children with heterozygous *INS* mutations is similar to those with K_{ATP} channel mutations, but they present at somewhat later ages.

- Although the diabetes is still diagnosed most often before 6 months of age, it can also occur up to a year of age or even later; therefore genetic testing should be considered in children with autoantibody negative diabetes presenting at early ages,[89,91,93,96] as well as in those with a MODY-like phenotype.
- Most heterozygous *INS* mutations are sporadic de novo mutations but about 20% of probands have a family history of autosomal dominant NDM.[91]

9.3.2 | Wolcott–Rallison syndrome

This rare autosomal recessive syndrome is the commonest cause of PNDM in highly inbred populations and characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction.[97,98] Wolcott–Rallison syndrome (WRS) is caused by biallelic mutations in the *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) gene, which encodes a protein involved in the regulation of the endoplasmic reticulum (ER) stress response. Pancreatic development is rather normal in the absence of the functional protein, but misfolded proteins accumulate within the endoplasmic reticulum after birth and eventually induce β-cell apoptosis. Although diabetes usually manifests during infancy, it might not present until 3–4 years of age. Diabetes may be the first clinical manifestation of the syndrome and, therefore, this diagnosis should be considered even in children with isolated PNDM, especially if they were born to consanguineous parents or from a highly inbred population.[99,100] Since the disease is recessively inherited, there is a 25% recurrence risk in siblings. Fulminant hepatic failure is the main cause of death in persons with WRS and currently there is no agent to reverse this abnormality[101]; however, recent reports indicate that liver

(with or without pancreas) transplantation can be life saving and improve the outcomes of individuals with this syndrome.[101–104]

9.3.3 | Neonatal diabetes due to GCK mutations

The enzyme glucokinase is considered the glucose sensor of the β-cells, as it catalyzes the rate-limiting step of glucose phosphorylation and therefore enables the β-cell to respond appropriately to the degree of glycemia.[105]

- Complete glucokinase deficiency secondary to mutations in both alleles, either homozygous or compound heterozygous, prevents the β-cells from secreting insulin in response to hyperglycemia.[106,107]
- Neonates present with severe IUGR, are usually diagnosed with diabetes during the first few days of life, and require exogenous insulin therapy. Apart from diabetes, they do not show any relevant extrapancreatic features.[106–113]

GCK is responsible for not more than 2%–3% of cases of PNDM overall,[47] but has an increased prevalence in regions with a high degree of consanguinity.[114] This type of PNDM is inherited in a recessive manner so the recurrence risk for future siblings is 25%. This diagnosis should be strongly considered in probands born to parents with asymptomatic mild hyperglycemia; therefore, measuring fasting blood glucose in the parents of any child with NDM, even when there is no known consanguinity or family history of diabetes, is often recommended.

Few studies have evaluated the risk of microvascular complications in NDM, but one study showed that individuals with KATP/PNDM or abnormalities in the insulin gene (*INS)* do not seem prone to severe eye complications even after a median diabetes duration of 24 years.[115]

10 | IPEX SYNDROME AND OTHER MONOGENIC CAUSES OF AUTOIMMUNE DIABETES

- Mutations in at least nine different genes are now known to cause autoimmune syndromes that can include neonatal and infancy-onset diabetes associated with pancreatic islet autoantibodies: *AIRE, CTLA4, FOXP3, IL2RA, ITCH, LRBA, STAT1, STAT3, and STAT5B.*
- These monogenic conditions that do cause autoimmune diabetes share basic features with pediatric T1D[15,116–118] and account for the previously mentioned rare cases of T1D in the first months of life.
- Rarely, some cases of diabetes with onset during the first 6 months of life have an autoimmune basis; it is now accepted that mutations in a range of genes related to immune function (such as *FOXP3*, *STAT3*, *or LRBA*) are at least as likely as T1D.

Mutations in the *FOXP3* gene are responsible for the immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome.[119,120] IPEX syndrome is clinically heterogeneous ranging from severe intrauterine forms to moderate phenotypes, as has been recently described in different cohorts.[117,121,122] Among male infants who present with diarrhea, eczema, autoimmune diabetes, immune deficiency, and/or life-threatening infection, mutations in *FOXP3* should be considered.[123,124] Treatment with immunosuppressive agents (sirolimus or steroids).[123,124] Alternatively, allogeneic hematopoietic stem cell transplantation (HSCT) with reduced-intensity conditioning is recommended.[125] Survival is similar with both immunosuppressant treatment and HSCT, but higher rates of disease-free survival and improved quality of life have been shown with HSCT.[126]

In addition to mutations in *FOXP3* "classic IPEX," there is a group with an "IPEX-like" phenotype with defects in other genes. Examples include individuals with heterozygous mutations in *CTLA4* causing autoimmune lymphoproliferative syndrome which can include autoimmune diabetes, enteropathy, cytopenias, and thyroiditis[127]; individuals with recessive mutations in the ubiquitin ligase gene (ITCH) present with multisystem autoimmune disease and facial dysmorphism[128]; individuals with bi-allelic mutations in *IL2RA* (interleukin 2 receptor subunit alpha) resulting in immunodeficiency 41 syndrome, with lymphoproliferation, other autoimmunity, and autoimmune diabetes,[129,130] as well as individuals with recessively inherited mutations in *LRBA* reported as a cause of immunodeficiency-8 with autoimmune enteropathy, T1D, autoimmune hypothyroidism, and autoimmune hemolytic anemia.[118]

The proteins encoded by the *STAT3*, *STAT1*, and *STAT5B* genes are transcription factors involved in the cellular response to cytokines and growth factors. Activating mutations in *STAT3* cause multiple autoimmune disease with enteropathy, hematological autoimmune disorders, autoimmune cytopenia, and autoimmune diabetes which often presents in the neonatal period.[116,131] Persons with gain of function mutations in *STAT1* present with chronic fungal infections including respiratory tract infections with a subset of people developing severe organ specific autoimmunity including T1D.[132] On the other hand, loss of function mutations in *STAT5B* are associated with disorders characterized by allergic or autoimmune manifestations.

Loss of function mutations in the *AIRE* gene cause polyendocrine autoimmune syndrome type 1 (APS1), characterized by chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency. In addition, 13% of individuals present with diabetes by 30 years of age.[128]

11 | OTHER CAUSES OF NEONATAL DIABETES

More than 30 genetic subtypes of NDM have been described. The clinical features seen in the more common causes of neonatal and infancy-onset diabetes are shown in Table 1. Pancreatic scanning is unreliable in neonates and so it is best to use functional tests of exocrine pancreatic function (fecal elastase and fecal fats) when assessing if pancreatic aplasia is present.[133,134] Apart from KATP-NDM and some persons with *SLC19A2* mutations causing thiamine-responsive

megaloblastic anemia (TRMA) syndrome,[135] all other causes need to be treated with subcutaneous insulin. Children with pancreatic aplasia/hypoplasia will also require exocrine pancreatic supplements.

11.1 | Genetic testing should be performed as soon as diabetes is diagnosed in a child aged less than 6 months

- All infants diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of monogenic NDM, as T1D is extremely rare in this subgroup.
- Genetic testing will allow diagnosis of a specific type of monogenic diabetes in over 80% of children whose diabetes is diagnosed before the age of 6 months. As discussed above, this will influence treatment as well as prediction of clinical features.
- It is no longer necessary to wait to see if diabetes resolves or for other features to develop, as major laboratories will offer comprehensive testing of all NDM subtypes as well as very rapid testing of subtypes that alter treatment.

12 | AUTOSOMAL DOMINANT FAMILIAL MILD HYPERGLYCEMIA OR DIABETES (MODY)

A familial form of mild diabetes presenting during adolescence or in early adulthood was first described many years ago.[10,136] Even though diabetes presented in young people, the disease clinically resembled elderly-onset non-insulin dependent diabetes and the newly recognized subtype of familial diabetes became known by the acronym MODY (maturity-onset diabetes of the young).[137] As MODY persons passed on the disease to their offspring following an autosomal dominant pattern of inheritance, it was quickly suspected that it might be a monogenic disorder.[138] MODY is by far the commonest type of monogenic diabetes. All currently known subtypes of MODY are caused by dominantly acting heterozygous mutations in genes important for the development or function of β-cells. Over the last few years, however, a number of forms of monogenic diabetes clinically and genetically different from MODY have been identified.[1] Individuals may harbor dominant mutations arising de novo; in such cases, a family history suggesting a monogenic condition is lacking.[41,90,139] These facts, along with a widespread lack of awareness, hinder clinical diagnosis so that the majority of children with genetically proven monogenic diabetes are initially misdiagnosed as having T1D[140,141] or T2D.[142,143] Although monogenic diabetes is uncommon, it accounts for 2.5%–6% of pediatric diabetes cases.[144–149]

- MODY syndromes are forms of monogenic diabetes characterized by impaired insulin secretion, with minimal or no defects in insulin action.[150]
- Most cause isolated diabetes and therefore may be misdiagnosed as either familial T1D or T2D.[142,151]
- Classic criteria for MODY include family history of diabetes; however, sporadic de novo mutations in several causative genes have been reported.[152]
- The different genetic subtypes of MODY differ in age of onset, pattern of hyperglycemia, and response to treatment.
- Three genes are responsible for the majority of MODY cases (*GCK*, *HNF1A*, and *HNF4A*) and will be described in some detail below.
- Most MODY subtypes will have a phenotype of isolated diabetes or stable mild fasting hyperglycemia, but some MODY genes have additional features such as renal cysts (see HNF1B below) or pancreatic exocrine dysfunction.[153]

At least 14 different genes have been reported to cause diabetes with a MODY-like phenotype (Table 2), and some panels will include all these genes or, possibly, also many other genes associated with exceedingly rare recessive causes. It is reasonable to consider including syndromic causes such as mitochondrial diabetes, as diabetes can often be the first presenting feature and a molecular diagnosis can thereby guide monitoring and treatment of other associated features. In the modern era of expanded testing by many different laboratories, caution must be used when interpreting test results, as often there is very little information available to support the causality of rare variants in uncommon subtypes.

13 | MILD FASTING HYPERGLYCEMIA DUE TO GLUCOKINASE GENE MUTATIONS (GCK-MODY, MODY2)

- GCK-MODY is the commonest subtype of monogenic diabetes in the pediatric diabetes clinic and its clinical phenotype is remarkably homogeneous among affected persons.
- In contrast to other subtypes of monogenic diabetes, persons with GCK-MODY regulate insulin secretion adequately but around a slightly higher set point than other people. As a result, they show nonprogressive mild hyperglycemia from birth.[154]
- HbA1c is mildly elevated but usually below 7.5% (59 mmol/mol).[155]
- Despite the mild fasting hyperglycemia, there is usually a small increment in blood glucose during an oral glucose tolerance test (OGTT) (<60 mg/dl or <3.5 mmol/L)[156] although this should not be considered an absolute criterion because of the variability of the OGTT.
- Since the degree of hyperglycemia is not high enough to cause osmotic symptoms, most cases are usually diagnosed incidentally when blood glucose is measured for another reason.
- The incidental finding of mild hyperglycemia (5.5–8 mmol/L or 100–145 mg/dl) in otherwise asymptomatic children and adolescents raises the possibility that they will subsequently develop T1D or T2D. In the absence of concomitant islet autoimmunity,

the risk of future T1D is minimal,[157] and a significant proportion will have a heterozygous mutation in *GCK*.[158] In peripubertal children and adolescents with a diagnosis of T2D, the lack of obesity or other signs of IR should raise concern about the diagnosis of MODY.

- Since blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely associated with chronic microvascular or macrovascular complications of diabetes.[159,160] and affected individuals do not generally require any treatment[161] except in the setting of pregnancy where an affected mother has an unaffected fetus and there is in utero evidence of accelerated growth.[162]
- When the clinical features of asymptomatic, long-standing, stable mild fasting hyperglycemia are present, specific testing of *GCK* is appropriate.

Very often, the affected parent remains undiagnosed or has been misdiagnosed with early-onset T2D. Measuring fasting glucose concentrations in apparently unaffected parents is important when considering a diagnosis of a *GCK* mutation. GCK-MODY may first be diagnosed during pregnancy; it represents ~2%–6% of cases of gestational diabetes and can be differentiated from gestational diabetes based on clinical characteristics and fasting glucose concentration.[163,164]

Of note, the presence of a *GCK* mutation does not protect against the concurrent development of polygenic T2D later in life, which occurs at a similar prevalence as in the general population.[165] *GCK*-PNDM may manifest in *GCK*-MODY families especially in the setting of consanguinity.

14 | FAMILIAL DIABETES DUE TO *HNF1A*-MODY (MODY3) AND *HNF4A*-MODY (MODY1)

- The possibility of monogenic diabetes should be considered whenever a parent of a child with diabetes also has diabetes, even if they are thought to have T1D or T2D.
- Glucose intolerance associated with HNF1A- and HNF4A-MODY usually becomes evident during adolescence or early adulthood. In the early stages of the disease, fasting blood glucose concentration may be normal, but there may be a large increment in blood glucose (>80 mg/dl or 5 mmol/L) after meals or at 2 h during an OGTT.[156]
- Over time, fasting hyperglycemia and osmotic symptoms (polyuria, polydipsia) present but they rarely develop ketosis because some residual insulin secretion persists for many years.
- Chronic complications of diabetes are frequent, and their development is related to the degree of glycemic management.[166]
- HNF1A-MODY is the most common form of monogenic diabetes that results in familial *symptomatic* diabetes, with heterozygous HNF1A mutations being about 10 times more frequent than heterozygous mutations in HNF4A.[167] Therefore, HNF1A-MODY is the first diagnostic possibility to be considered in families with autosomal dominant symptomatic diabetes.
- Persons with HNF1A-MODY demonstrate an impaired incretin effect and inappropriate glucagon responses to OGTT.[168]
- Despite the association of *HNF1A* mutations with microvascular complications, recent data suggest that timely initiation of treatment with SUs is associated with lower rate of microvascular complications than T1D.[169] *HNF1A* mutations are also associated with an increased frequency of cardiovascular disease and mortality.[170]

Mutations in *HNF1A* show a high penetrance so that 63% of mutation carriers develop diabetes before 25 years of age, 79% before age 35, and 96% before 55 years.[1] The age at diagnosis of diabetes is partly determined by the location of the mutation within the gene.[171,172] Persons with mutations affecting the terminal exons (8 to 10) are diagnosed, on average, 8 years later than those with mutations in exons 1 to 6. On the other hand, exposure to maternal diabetes in utero (when the mutation is maternally inherited) brings forward the age at onset of diabetes by about 12 years.[156] In the pediatric population, diabetes in *HNF4A* mutation carriers tends to appear at a similar age to persons with mutations in *HNF1A*.[146]

Some differential clinical characteristics may be noted between persons with mutations in *HNF4A* and *HNF1A*; however, they do not often help in the choice of genes to be sequenced and it would be preferable to test all genes simultaneously with NGS whenever possible.[173]

- Persons with *HNF1A* mutations typically have a low renal threshold for glucose reabsorption due to impaired renal tubular transport of glucose and may present postprandial glycosuria before developing significant hyperglycemia.[174]
- In addition to diabetes, carriers of the p.Arg76Trp (R76W) mutation in *HNF4A* present with an atypical form of Fanconi syndrome including hypercalciuria and nephrocalcinosis.[175]
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia.[176] In this case, hyperinsulinism typically remits during infancy and individuals develop diabetes from adolescence.[177,178] Hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers[179] but this is very uncommon.

Persons with both *HNF1A* and *HNF4A*-diabetes can initially be treated with diet although they will have marked postprandial hyperglycemia with high carbohydrate food.[156]

- Most will need pharmacological treatment as they show progressive deterioration in glycemic management. They are extremely sensitive to SUs,[180] which usually allow better glycemic management than that achieved with insulin, especially in children and young adults.[181]
- The initial dose of SUs should be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. As long as there are

no problems with hypoglycemia, they can be maintained on low-dose SUs (e.g., 20–40 mg gliclazide daily) for decades.[182,183]
- If there is hypoglycemia despite dose titration of a once or twice daily SU preparation, a slow-release preparation or meal time doses with a short-acting agent such as a meglitinide may be considered.[184] A randomized controlled trial comparing a glucagon-like peptide receptor agonist (GLP1RA) with a SU demonstrated lower fasting glucose in those treated with the GLP1RA.[168]

15 | DIABETES ASSOCIATED WITH EXTRA-PANCREATIC FEATURES

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features,[185] or in young-onset diabetes when consanguinity is known or suspected, even when syndromic features are not obvious.[186] These syndromes may either cause NDM (Table 1) or present later in life (see below). The Online Mendelian Inheritance in Man website (www.ncbi.nlm.nih.gov/omim or www.omim.org) can help with clinical features and to know if the gene for a particular syndrome has been defined hence molecular genetic testing is available. Genetic testing for some of these conditions is available on a research basis at www.euro-wabb.org.[187] The most common syndromes usually presenting beyond infancy are described in some detail below. A number of rare syndromes that include diabetes may also be tested through a gene panel approach (for example, see https://www.diabetesgenes.org/).

15.1 | Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD) syndrome (WFS)

The combination of diabetes and progressive optic atrophy below 16 years of age is diagnostic of this autosomal recessive syndrome.[188] Non-autoimmune, insulin requiring diabetes, presenting at a mean age of 6 years, is usually the first manifestation of the disease.[189] Other reported features, including sensorineural deafness, central diabetes insipidus, urinary tract dysfunction, and neurological symptoms that develop later in a variable order even within the same family.[190–192] Many individuals with WFS are initially diagnosed as having T1D and subsequent loss of vision, which occurs ~4 years after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy.[193,194] Persons with WFS die at a median age of 30 years, mainly from neurodegenerative complications. At least 90% of these people harbor biallelic mutations in the *WFS1* gene.[195] This gene encodes WFS1, which is an endoplasmic reticulum (ER) transmembrane protein important for the negative regulation of ER stress and the maintenance of cellular calcium homeostasis.[196] Preclinical studies in cell and animal models suggest that therapeutic strategies targeting ER calcium homeostasis may be beneficial. However, a recent trial of using dantrolene sodium in 19 WFS subjects showed no significant improvement in β-cell, retinal or neurological function.[197]

A second variant of the syndrome (WFS2) has been described in association with mutations in *CISD2* gene.[198] Persons with this rare variant do not develop diabetes insipidus but present with additional symptoms including a bleeding diathesis and peptic ulcer disease.

The current management of WFS involves symptomatic treatment of the associated features with no agents to cure or slow the disease progression.

15.2 | Renal cysts and diabetes (RCAD) syndrome (HNF1B-MODY or MODY5)

Although initially described as a rare subtype of familial diabetes, it is now clear that persons with heterozygous mutations in *HNF1B* rarely present with isolated diabetes.[199] In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all persons with *HNF1B* mutations or gene deletions[139] and constitute the main presentation in children, even in the absence of diabetes.[200–202] Genital tract malformations (particularly uterine abnormalities), hyperuricemia, and gout can also occur, as well as abnormal liver function tests.[199] Diabetes develops later, typically during adolescence or early adulthood[203,204] although TNDM has been reported in a few cases.[23,203] In addition to insulin deficiency related to pancreatic hypoplasia,[205] affected persons also show some degree of hepatic IR,[206] which explains why they do not respond adequately to SU treatment and require early insulin therapy.[1] Moreover, mutation carriers have lower exocrine pancreatic function with reduced fecal elastase; this involves both ductal and acinar cells.[207] Therefore, the phenotype of RCAD is highly variable even within families sharing the same *HNF1B* mutation and therefore this diagnosis should be considered not only in the diabetes clinic but also in other clinics (nephrology, urology, gynecology, etc.). In people with diabetes found to have renal cysts, imaging of the pancreas is indicated, since the absence of the pancreatic body and/or tail is highly indicative of HNF1B-MODY.[208] Fecal elastase should also be measured, as this is always abnormal in persons with HNF1B-MODY.[207] Importantly, a family history of renal disease or diabetes is not essential to prompt genetic testing, as de novo mutations and deletions of this gene are common (one-third to two-thirds of cases).[139,200]

15.3 | Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen (<1%) in children and adolescents[209] as most affected persons develop diabetes as young or middle-aged adults. The most common form of mitochondrial diabetes is caused by the m.3243A>G mutation in mitochondrial DNA. Diabetes onset is usually insidious but ~20% may have an acute presentation, including diabetic ketoacidosis.[210] Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy.[209,211,212] Mitochondrial diabetes should be suspected in persons presenting

with diabetes and maternally inherited sensorineural hearing loss, or diabetes and progressive external ophthalmoplegia. Interestingly, the same m.3243A>G mutation also causes a much more severe clinical syndrome known as MELAS (myopathy, encephalopathy, lactic acidosis, and stroke).[213]

Persons with mitochondrial diabetes may initially respond to diet or oral hypoglycemic agents but often require insulin treatment within months or years. Metformin should be avoided as it interferes with mitochondrial function and may trigger episodes of lactic acidosis.[214]

The penetrance of diabetes in mutation carriers depends on age, but is estimated to be above 85% at 70 years.[210] Affected males do not transmit the disease to their offspring. In contrast, females transmit the mutation to all their children, although some may not develop the disease.[1] In addition to the m.3243A>G mutation, early-onset diabetes (even in infancy) has been reported in other less common mitochondrial disorders such as Kearns-Sayre syndrome[215] and Pearson syndrome.[216]

15.4 | Diabetes secondary to monogenic diseases of the exocrine pancreas

Heterozygous mutations in *CEL*, which encodes a pancreatic lipase, cause CEL-MODY or MODY8, an autosomal dominant disorder of pancreatic exocrine insufficiency and diabetes.[153] Importantly, the exocrine component of the syndrome is evident in childhood, 10–30 years before diabetes develops, and can be revealed by reduced fecal elastase and/or pancreatic lipomatosis.[217,218] Diabetes typically develops in the 30–40s together with pancreatic cysts.[218] The *CEL* gene is highly polymorphic and extremely difficult to sequence. El Jellas et al recently described how to diagnose CEL-MODY.[219] The disease mechanism of CEL-MODY involves protein misfolding/aggregation, endoplasmic reticulum stress, and proteotoxicity.[220–223] Other autosomal dominant monogenic diseases mainly affecting the exocrine pancreas that can lead to diabetes sooner or later include cystic fibrosis (*CFTR*), hereditary pancreatitis (*PRSS1* and *SPINK1*)[224] and pancreatic agenesis/hypoplasia (*GATA6*).[134]

15.5 | Syndromic diabetes due to TRMT10A and DNAJC3 deficiencies: oxidative stress, apoptosis in β-cells

Mutations in TRMT10A, a nuclear tRNA methyltransferase, are associated with a novel syndrome of young-onset diabetes mellitus or impaired glucose metabolism, microcephaly, intellectual disability, short stature, and delayed puberty (OMIM 616013). To date, five families are described in the literature with a total of 11 people with a mutation. Phenotypes are heterogenous with most individuals presenting with impaired glucose homeostasis, microcephaly, short stature, seizures, and intellectual disability.[225]

DNAJC3 mutation, which is associated with DM and multisystemic neurodegeneration, have been described. Familial case of DNAJC3 mutation manifesting as juvenile-onset DM, hypothyroidism, multisystemic neurodegeneration, short stature, and sensorineural hearing loss with the new finding of pancreatic fibrosis and atrophy.[226]

16 | MONOGENIC INSULIN RESISTANCE SYNDROMES

- The cardinal features of IR syndromes include moderate to severe acanthosis nigricans in association either with markedly increased insulin concentrations (fasting insulin >150 pmoL/L) or, where there is diabetes, increased insulin requirements, usually in the absence of a corresponding degree of obesity.
- Three different subtypes are described, based on the underlying pathogenic mechanism: primary insulin signaling defects, IR secondary to adipose tissue abnormalities, and IR as a feature of complex syndromes.[227]
- Clinical and biochemical characterization of persons with severe IR may be used to guide genetic testing (Table 3).
- In contrast with monogenic syndromes of β-cell failure, hyperglycemia and diabetes tend to occur later in the genetic syndromes of severe IR and may not be a feature before the onset of puberty,[228] except for Donohue syndrome.

The phenotypes of monogenic IR syndromes tend to be more pronounced in females, who may present during adolescence with significant ovarian hyperandrogenism. The physical appearance of the partial lipodystrophies can also be less pronounced in males and so the presentation is more common in females who can present with features similar to those seen in polycystic ovarian syndrome.

16.1 | Primary insulin signaling defects due to mutations in the insulin receptor (INSR) gene

INSR mutations are responsible for a number of rare IR syndromes.[229,230] Leptin levels are low, but adiponectin levels are paradoxically normal or elevated since insulin normally inhibits adiponectin secretion.[231] There is a spectrum of severity, depending on the effect of the mutation on the signaling function of the receptor. The most severe forms are associated with either homozygous or compound heterozygous mutations in the INSR gene responsible for Donohue and Rabson-Mendenhall Syndromes. In Donohue Syndrome this leads to almost complete loss of insulin action at the cellular level and in Rabson-Mendenhall Syndrome, where there is some residual insulin signaling, the phenotype can be milder.[232] Infants with Donohue Syndrome are born small for gestational age and develop diabetes in infancy with insulin concentrations over 1000 pmoL/L, often in association with cardiomyopathy and hypertrichosis. Postprandial hyperglycemia may be severe, and present early in life, but is usually accompanied by fasting hypoglycemia. There is no effective treatment, and the majority of infants sadly succumb to infection, or

cardiac complications during the first year of life. Children with Rabson–Mendenhall Syndrome may not present until later in childhood, with failure to thrive, gingival hyperplasia, acanthosis nigricans, hyperandrogenism, and insulin resistant diabetes requiring very high doses of insulin developing during adolescence.[229,233]

Type A IR Syndrome is the mildest form and results most commonly from a heterozygous mutation in the *INSR* gene and is inherited in an autosomal dominant manner.[229] Diabetes is rare before adolescence, but there can be significant ovarian hyperandrogenism and acanthosis nigricans during puberty.

The management of hyperglycemia in persons with *INSR* mutations can be challenging as insulin is largely ineffective even at high does. Insulin sensitizers such as metformin may be tried initially but most will need extraordinarily high doses of insulin, with limited effect.[229] As an alternative therapeutic method for young children, recombinant human IGF-I has been reported to improve both fasting and postprandial glycemia although long-term effects on survival remain unclear.[234,235] Recently, a trial showed benefits of long-term treatment with metreleptin in persons with Rabson-Mendenhall Syndrome.[236] Use of SGLT2i has also been reported to be beneficial in improving hyperglycemia.[237,238] For females, the hirsutism resulting from ovarian hyperandrogenism should be managed using similar strategies as for polycystic ovarian syndrome.[239]

16.2 | Monogenic lipodystrophies

Lipodystrophies are characterized by a partial or complete reduction in adipose tissue, which results in decreased adipokine levels and IR.[240,241] Mutations in either *AGPAT2* or *BSCL* account for ~80% of cases of congenital generalized lipodystrophy (Berardinelli–Seip syndrome).[242] These are recessively inherited disorders characterized by an almost complete absence of subcutaneous and visceral fat. The clinical features are often apparent at birth. Inability to store excess dietary fat results in ectopic fat deposition in the liver, with hepatic steatosis that may progress to cirrhosis.[241] Diabetes can manifest in early infancy, but there then can be a period of remission until late childhood.

In contrast, a clinical diagnosis of familial partial lipodystrophy (FPLD) is usually made after puberty where there is failure to gain subcutaneous fat in the extremities and lower trunk during puberty, in combination with progressive accumulation of subcutaneous adipose tissue in the face and around the neck.[241,243] Heterozygous mutations in *LMNA* or *PPARG* account for ~50% of cases.[240] Visceral fat is greatly increased in addition to hyperinsulinemia, hypertriglyceridemia, and decreased HDL-cholesterol levels.[244] Diabetes usually appears in late adolescence or early adulthood. More recently, there has been opportunity to make a genetic diagnosis in the offspring of persons with FPLD. In theory, this permits early intervention with lifestyle recommendations and screening for co-morbidities in the hope that the development of co-morbidities can be delayed but it is too early to tell whether this approach will be effective.

More rarely, lipodystrophy may occur as part of a multi-system disorder. A mutation in POLD1, a universal DNA polymerase causes subcutaneous lipodystrophy in combination with diabetes, deafness, mandibular hypoplasia, and hypogonadism in males.[245] SHORT syndrome (short stature, hypermobility of joints, ocular depression, Rieger's anomaly, teething delay) with partial lipodystrophy, is caused by a hot spot mutation in *PIK3R1* which has a central role in the insulin-signaling pathway and growth factor resistance.[246–248] Mutation carriers of the dominant-negative mutation in *PIK3R1* seem to be protected from obesity and hepatic steatosis but not diabetes,[249] and the disease mechanisms is associated with unfolded protein response and reduced sensitivity to ER stress-dependent apoptosis.[250]

The mainstay of therapy for lipodystrophy is dietary intervention with a low-fat, calorie-neutral diet,[241] and an expert dietician as part of the multidisciplinary team is of paramount importance. In partial lipodystrophy, insulin sensitizers such as metformin and glitazones may be initially effective[251] but glitazones may exacerbate accumulation of ectopic fat in the face and neck.[228] More recently, therapy with recombinant leptin, given by daily subcutaneous injection, has been shown to be well tolerated, with sustained improvements in hypertriglyceridemia, glycemic management, and liver volume.[252] Efficacy in the partial forms of lipodystrophy is less clear, but where conventional therapy for diabetes and hypertriglyceridemia has not been successful, adjunctive therapy with metreleptin should be considered.[253]

16.3 | Ciliopathy-related insulin resistance and diabetes

16.3.1 | Alström syndrome

This autosomal recessive disorder shares symptoms with Bardet-Biedl syndrome (see below), including progressive visual impairment related to cone-rod dystrophy, sensorineural hearing loss, obesity, and diabetes mellitus. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of cognitive impairment.[254] More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function.[255] Persons with Alström syndrome (ALMS) usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly-progressive insulin-resistant diabetes.[256] Lifestyle intervention can initially ameliorate the metabolic abnormalities.[257]

16.3.2 | Bardet-Biedl syndrome (BBS)

This disorder is characterized by intellectual disability, progressive visual impairment due to cone-rod dystrophy, polydactyly, obesity, diabetes mellitus, renal dysplasia, hepatic fibrosis, and hypogonadism. Obesity is found in almost every affected individual, while diabetes

affects less than 50%.[258] While the syndrome shares some similarities with Lawrence-Moon syndrome, these two disorders can be distinguished by the presence of paraplegia and the absence of polydactyly, obesity, and diabetes mellitus in Lawrence-Moon syndrome. Terms such as Lawrence-Moon-Bardet-Biedl or Lawrence-Moon-Biedl syndrome should therefore be avoided. Bardet-Biedl syndrome has been linked to 18 different genetic loci, referred to as *BBS1* to *BBS18*.[259,260] The majority of cases are autosomal recessive,[261] but triallelic inheritance has been reported.[262] Genetic diagnostic laboratories and detailed clinical recommendations for persons with ALMS and BBS are present at http://www.euro-wabb.org.

17 | CONCLUSIONS

Advances in molecular genetics have led to the identification of genes associated with many clinically identified subgroups of diabetes. Molecular genetic testing should now be considered an essential clinical diagnostic tool that can help define the diagnosis and determine the appropriate treatment of children with diabetes. Although the cost of NGS continues to drop, diagnostic genetic testing should be limited to those persons with diabetes who are likely to harbor a mutation based on the suggestive clinical features described above.

CONFLICT OF INTEREST

Dr Michel Polak MD, PhD has acted as scientific advisor for the development of the glibenclamide-glyburide suspension named AMGLIDIA in the European Union. The other authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Greeley SAW, Polak M, Njølstad PR, et al. ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1188-1211. doi:10.1111/pedi.13426

Accepted: 7 November 2022
DOI: 10.1111/pedi.13453

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Management of cystic fibrosis-related diabetes in children and adolescents

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KEYWORDS: adolescents, CFTR modulator, children, cystic fibrosis related diabetes, HEMT therapy

1 | WHAT IS NEW OR DIFFERENT?

- For some people with cystic fibrosis (CF), a new and life-changing era has begun; however, for others, existing disparities have only increased. The lives of persons with CF (PwCF) have been profoundly changed by the advent of highly effective CF transmembrane conductance regulator (CFTR) modulator therapy (HEMT) (elexacaftor/tezacaftor/ivacaftor combination therapy or ivacaftor alone in specific *CFTR* mutations), small molecule compounds that directly correct the basic defect of the CFTR channel and restore channel function.
- Emerging technologies for the management of diabetes including advanced insulin pumps and continuous glucose monitoring (CGM) have improved markedly since the 2018 ISPAD guidelines and will improve care for people with cystic fibrosis-related diabetes (CFRD).

- The guidelines have been updated to recommend insulin pump and CGM therapy for CFRD as appropriate and to address what is known regarding the effect of HEMT therapy on CFRD.
- The screening and therapy sections have been revised and expanded and new sections on hypoglycemia and health related quality of life (HRQoL) have been added.

  Unfortunately, these life-changing and paradigm-shifting medications and technologies, while saving many lives, are dramatically worsening the disparities already affecting PwCF. Disparities will likely come to be a defining feature of the care of PwCF and CFRD going forward due to both HEMT (which cost approximately USD 200,000 per year) and advanced insulin pumps and CGM technology. People of non-northern European descent are more likely to belong to groups that do not respond to HEMT therapy and are less likely to be provided access to advance diabetes technology even when income is equal, creating a worsening double disparity.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | Background/pathophysiology

- CFRD is the most common non-pulmonary comorbidity in CF and increases mortality. **B**
- The pathophysiology of CFRD is unique and complex but is primarily driven by insulin insufficiency and differs from type 1 diabetes (T1D) and type 2 diabetes (T2D). **A**
- The cause of insulin insufficiency in CF is multifactorial and incompletely understood, but exocrine pancreas damage and dysfunction, inflammation, genetic susceptibility, and nutritional state all contribute to beta cell dysfunction. **B**
- CFRD is often clinically silent and clinical decline can occur before diabetes is diagnosed. **C**
- Few individuals with CF have fully normal glucose tolerance (NGT) and even when fasting and 2-h blood glucose levels (BGLs) are normal on an oral glucose tolerance test (OGTT) variable intermittent postprandial hyperglycemia can often be detected by CGM. **B**
- Early CFRD is typically asymptomatic and characterized by normal fasting BGLs. BGLs can vary over time depending on underlying health and medical therapy, but typically worsen with age. **B**
- HEMT does not immediately cure established CFRD; however further data are still needed to determine the long-term effects. **C**

2.2 | Hypoglycemia

- Hypoglycemia is common in CF and can occur even in the absence of CFRD or insulin therapy. **B**
- Post OGTT hypoglycemia is common. **B**
- It is advisable to check for hypoglycemia in PwCF and advice provided to eat at the end of an OGTT. **E**

2.3 | Diagnosis

- Diagnosis of CFRD is made using American Diabetes Association (ADA) criteria during a period of stable baseline health **E**
  - 2-h BGL on OGTT ≥11.1 mmol/L (200 mg/dl)
  - Fasting BGL ≥7.0 mmol/L (126 mg/dl)
    - Fasting BGL ≤7.0 mmol/L (126 mg/dl) does not rule out diabetes in CF
  - HbA1C ≥ 48 mmol/mol (6.5%)
    - HbA1C < 48 mmol/mol (6.5%) does not rule out diabetes in CF
  - Random BGL ≥11.1 mmol/L (200 mg/dl) with classic symptoms of diabetes
- Onset of CFRD is defined as the first time a person with CF meets criteria for CFRD, even if glucose tolerance subsequently improves. **E**
- Diagnosis of diabetes can be made with acute illness (intravenous antibiotics/systemic glucocorticoid therapy) if fasting BG ≥7 nmol/L (126 mg/dl) or 2 h postprandial BG ≥11.1 mmol/L (200 mg/dl) persist for more than 48 h. **E**
- Diagnosis of diabetes can be made in an individual on overnight enteral feedings when mid or post-feeding BG readings are ≥11.1 mmol/L (200 mg/dl) on two separate days. **E**

2.4 | Screening

- HbA1C is not a recommended screening test for CFRD due to its low sensitivity. **C**
- Screening for CFRD should be performed using the 2-h 75 g (1.75 g/kg) OGTT. **B**
- Yearly OGTT should begin at least by age 10 years. **B**
- BGLs should be measured at minimum at fasting and 2 h on OGTT. **B**
- Consideration should be given to utilizing 1-h BGL measurement on OGTT, but there is insufficient evidence to recommend use at this time. **C**
- PwCF who are pancreatic sufficient have a lower risk of CFRD than those who are pancreatic insufficient but still higher than the general population; those with NGT may have OGTT screening every 3–5 years if deemed appropriate by the managing team. **B**
- There is inadequate evidence to recommend other forms of screening at this time. **E**
- Fasting BGL is not recommended for screening for CFRD due to low sensitivity. **B**
- Screening for gestational diabetes is recommended at both 12 to 16 weeks and 24 to 28 weeks gestation in pregnant women without known CFRD, using a 2-h 75 g OGTT with BG measures at 0,1, and 2 h. **E**
- Post-pregnancy screening for CFRD using a 2 h 75 g fasting OGTT is recommended 6 to 12 weeks after the end of pregnancy in women with diabetes first diagnosed during pregnancy.

- PwCF who have pulmonary exacerbations requiring IV antibiotics or glucocorticoids should be screened with fasting and 2-h postprandial BGLs for 48 h. **E**
- For PwCF on enteral feeds it is advisable to screen with mid and immediate post-feeding BGLs levels at the time of initiation of enteral feedings. Elevated BGLs detected by self-monitoring of blood glucose (SMBG) or CGM require confirmation at a certified laboratory. **E**
- PwCF without diabetes who are undergoing organ transplantation should be screened preoperatively with 2-h 75 g fasting OGTT if they have not had CFRD screening in the last 6 months. BGLs should be monitored closely in the perioperative period and until hospital discharge. **E**
- Screen for islet autoantibodies in the following scenarios: CFRD diagnosis <10 years of age, presentation in diabetic ketoacidosis (DKA), immediate family history of autoimmunity, or personal history of other autoimmune disease. **E**
- There is inadequate evidence to recommend the use of CGM or other forms of screening to replace OGTT at this time, but additional research is needed. **C**
- OGTT continues to have barriers to full use and additional research to improve CFRD screening is needed. **B**
- There is inadequate evidence at this time to alter CFRD screening based on use of highly effective CFTR modulator therapy. **E**

2.5 | Pregnancy

- Diagnosis of gestational diabetes (GDM) should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study group. New guidelines are anticipated in 2022 and these recommendations should be considered a placeholder until the updated guidelines are released. Diagnosis is based on 0, 1, and 2 h glucose levels with a 75 g OGTT if any one of the following is present: **E**
  - Fasting BGL >/= 5.1 mmol/L (92 mg/dl)
  - BGL1 >/= 10.0 mmol/L (180 mg/dl)
  - BGL2 >/= 8.5 mmol/L (153 mg/dl)
- Women with CF who have GDM, but no history of pre-existing CFRD, are not considered to have CFRD, but should be screened for CFRD 6–12 weeks after the end of pregnancy. **E**

2.6 | Treatment

- PwCF and CFRD (PwCFRD) should ideally be seen quarterly by a specialized multidisciplinary team with expertise in diabetes and CF. **E**
- PwCFRD should receive ongoing diabetes self-management education from diabetes education programs that meet national standards. **E**
- PwCFRD should be treated with insulin therapy. **B**
- Insulin pump therapy should be considered for individuals with CFRD requiring intensive insulin therapy, when accessible and appropriate, including partial closed loop therapies. **C**
- In certain cases (e.g., refusal of insulin therapy in asymptomatic individuals diagnosed by annual screening, but without fasting hyperglycemia) a trial of oral diabetes agents could be considered under close observation. **C**
  - Other oral diabetes drugs like metformin, sitagliptin, empagliflozin are in use in individual cases in single CF centers. However, there remains inadequate information to recommend the use of these diabetes drugs in CF. Further research is needed and ongoing. **E**
- PwCFRD who are on insulin should perform SMBG at least four times a day. For many individuals, more frequent monitoring is necessary. **E**
- Use of CGM in PwCFRD on insulin/anti-hyperglycemic medications is desirable and may be used as an alternative to SMBG. **B**
- PwCFRRD should strive to attain BG goals and time in range on CGM as per the ADA recommendations for all people with diabetes. More or less stringent goals may be indicated for persons early in the disease course or who experience significant or repeated hypoglycemia, and individualization is important. **E**
- HbA1c, as a measure of average glycemia, is recommended quarterly for persons with CFRD to guide insulin therapy decisions. **E**
  - For most PwCFRD the HbA1c treatment goal is ≤7% (53 mmol/mol) to reduce the risk of microvascular complications, bearing in mind that less stringent goals may be indicated for PwCF who experience significant or repeated hypoglycemia, and thus individualization is important. **C**
- Medical nutrition therapy is essential to the management of CFRD as in all forms of diabetes, but should follow CF guidelines for dietary therapy, with individualization based on person-specific weight/BMI goals. **E**
- Evidence-based guidelines for nutritional management of all PwCF are recommended for people with CFRD. **E**
- Nutritional management of diabetes alone without medical therapy is not recommended. **E**
- PwCFRD should be advised to do moderate aerobic exercise for at least 150 minutes per week. **E**

2.7 | Complications

- Education on symptoms, prevention, and treatment of hypoglycemia is recommended for all PwCF and their caregivers. **E**
- PwCFRD on insulin or oral hypoglycemic agents and their caregivers should be provided glucagon therapy and appropriate education. **E**
- PwCFRD should have their blood pressure measured every visit per ADA guidelines. If abnormal blood pressure is discovered, it should be repeated on a separate visit. **E**
- CFRD causes microvascular complications of diabetes including retinopathy, nephropathy and neuropathy. **B**

- Yearly screening for microvascular complications of diabetes is recommended starting at 5 years from diagnosis, or if diagnosis date is unknown, at the onset of fasting hyperglycemia. **E**
- PwCFRD diagnosed with hypertension or microvascular complications should receive standard treatment as recommended by the ADA for all people with diabetes except there should be no restriction of sodium or generalized restriction of protein. Inadequate evidence exists to alter these recommendations for those on HEMT therapy. **E**
- Rates of obesity and overweight are increasing in CF. **C**
- There is inadequate evidence at this time to recommend routine screening for macrovascular complications in people with CFRD and pancreatic insufficiency (PI). **E**
- Yearly lipid screening is recommended in people with CFRD and pancreatic sufficiency (PS). **E**
- Lipid screening is recommended every 5 years in PwCF and PI according to general population guidelines for low-risk individuals. **E**
- The experience of PwCF and their families should be incorporated into designing CFRD management approaches. **E**

3 | INTRODUCTION

Cystic Fibrosis (CF) was the most common fatal single-gene disorder in Caucasians. However, CF is found in non-Caucasians, including people of 100% African descent, and the prevalence of CF varies greatly from country to country and within regions of a single country.[1] It is caused by autosomal recessive mutations in CFTR the gene that encodes the anion channel, CFTR. CF is a multisystem disease characterized by chronic recurrent pulmonary infection and subsequent pulmonary function decline, accompanied by exocrine and endocrine pancreatic failure, gastrointestinal dysfunction, malnutrition, liver disease, and elevated risk for osteoporosis. Death occurs secondary to pulmonary disease. While just 50 years ago affected individuals seldom reached adulthood, steady improvements in care have increased longevity and it is now possible to see PwCF living into their 70s and beyond.

CFRD is the most common non-pulmonary comorbidity in CF and worsens nutritional status, increases pulmonary function decline, and increases mortality.[2–4] There are important pathophysiologic differences between CFRD, T1D, and T2D which necessitate a unique approach to management of CFRD. PwCF may have CF liver disease and/or chronic and acute inflammation which can drive fluctuating levels of insulin resistance and increase risk for CFRD. Additionally, some PwCF may require high caloric intake and may experience malabsorption, malnutrition, and abnormal gut motility including delayed gastric emptying, all of which complicate the management of diabetes in ways not typical in other populations.

The emergence of HEMT therapy has markedly improved pulmonary function and nutritional status and has dramatically decreased need for hospitalization and lung transplantation in PwCF who are eligible for these therapies. The full effects of these therapies on the natural history, pathogenesis, and future prevalence of CFRD are yet not fully understood. Further information on correctors' impact on CFRD can be found in Section 5.4.

3.1 | Diagnostic criteria for CFRD and abnormal glucose tolerance

The diagnostic criteria for CFRD were updated in 2010 in North America by the CFRD Guidelines Committee in a position statement co-sponsored by the ADA and the Cystic Fibrosis Foundation and endorsed by the Pediatric Endocrine Society.[5] At this time there is inadequate available evidence to support alternative cut offs for CFRD. Therefore, current diagnostic guidelines are identical to those used to diagnose other forms of diabetes, including HbA1c as a diagnostic criterion. Unlike other types of diabetes, however, low or normal HbA1c levels do not exclude the diagnosis of CFRD.[6,7]

Unlike other forms of diabetes, OGTT is the primary method of diagnosis in CF. CFRD is part of a spectrum of progressive glucose tolerance abnormalities defined by a standard OGTT (Table 1). Few individuals with CF have truly NGT when compared to people without CF.[8,9] Even when the fasting and 2-h OGTT glucose levels are normal, elevations in mid-OGTT glucose levels are common, ß-cell function is impaired, and variable, intermittent postprandial hyperglycemia can often be detected at home by CGM.[10–12] Early diabetes is characterized by normal fasting BGLs, but over time fasting hyperglycemia develops. Isolated-impaired fasting glucose (IFG) is sometimes present in PwCF but the significance is unclear.[13,14]

The onset of CFRD is defined as the first time a PwCF meets diagnostic criteria for diabetes, even if glucose tolerance subsequently appears to improve. Microvascular disease and mortality correlate with the duration of diabetes that includes these early years when diabetes appears to wax and wane.[15] This is consistent with a general pattern of progressive deterioration of glucose tolerance as individuals with CF get older.[16] However, the natural history can be variable[17,18] and dependent upon acute changes in pulmonary and infectious status. It is possible that HEMT may alter this course, but at this time there is insufficient evidence to recommend changes in this guideline for those treated with HEMT.

Hyperglycemia is common during pregnancy in women with CF because of the combination of increased insulin resistance and underlying insulin insufficiency.[19] Diagnosis of gestational diabetes should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study group. New guidelines are anticipated in 2022 and the recommendations in this document should be considered to be a placeholder until the updated guidelines are released. Diagnosis is based on 0, 1, and 2 h BG levels with a 75 g OGTT if any one of the following is present: Fasting BG >/-= 5.1 mmol/L (92 mg/dl), or PG1 >/= 10.0 mmol/L (180 mg/dl), or 2 h PG >/= 8.5 mmol/L (153 mg/dl). However, women with CF who have gestational diabetes and who do not meet diagnostic criteria for diabetes before or after pregnancy are not considered to have CFRD.

Category	FPG	2-h glucose	Notes
Normal (NGT)	<7.0	<7.8	All glucose levels <11.1
Indeterminate (INDET)	<7.0	<7.8	Mid- OGTT glucose >/= 11.1
Impaired (IGT	<7.0	7.8–11.1	
CFRD FH-	<7.0	>/= 11.1	
CFRD FH	>/=7.0		
IFG	6.1–6.9	<7.8	All glucose levels <11.1

TABLE 1 Abnormal glucose tolerance categories in CF

Note: Glucose levels reported as mmol/L – multiply by 18 to convert to mg/dl.
Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; FH, fasting hyperglycemia; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

In PwCF with pulmonary exacerbations requiring intravenous antibiotics or use of systemic glucocorticoids a diagnosis of CFRD is confirmed when fasting BG ≥126 mg/dl (≥7 mmol/L) or 2-h postprandial BGL ≥200 mg/dl (11.1 mmol/L) are detected and persist for at least 48 h, or with 2 diagnostic BGL values on separate days. In individuals on overnight enteral feedings, CFRD is diagnosed when mid- or post-feeding BG readings are ≥200 mg/dl (11.1 mmol/L) on 2 separate days.

4 | INCIDENCE AND PREVALENCE

People with CF have higher incidence and prevalence of diabetes than any other age matched group. CFRD can occur at any age, including infancy, but prevalence increases markedly with age.

The European Cystic Fibrosis Patient Registry (ECFSPR) data from 2008 to 2015 reported that prevalence increased with increasing age group: < 10 years 0.8%; 10–19 years 9.7%; 20–29 years 24.1%; and ≥ 30 years 32.7%; total prevalence of CFRD was 21.6%. The US Cystic Fibrosis Foundation (CFF) Registry data from 2020 are similar showing ∼20% of 20 year olds, 30% of 30 year olds and just under 40% of 40 year olds had a diagnosis of CFRD.[20,21] Unfortunately, both the ECFSPR and the CFF data may underestimate CFRD prevalence. The ECFSPR records insulin use as a proxy for CFRD and not everyone with CFRD is on insulin. The US CFF registry records screening results, but screening rates are consistently <70% teens and < 40% in adults.[21]

Data from Denmark and from the University of Minnesota in the US (UMN) represent the most comprehensive CFRD incidence and prevalence data available.[6,22] These data reveal an age-dependent incidence of 4%–9% per year in Denmark and 2.7 cases per 100 individual years at UMN. UMN also found diabetes in <5% of children under 10 years, 15%–20% of adolescents, 40% of 20–39 years and > 50% of those over 40 years. CFRD is more common with female sex, PI, and severe genotypes, with up to 80% in older people with severe genotypes.[20]

5 | PATHOPHYSIOLOGY OF CFRD

The mechanisms underlying CFRD are complex. Insulin secretion defects are present in essentially all individuals with CF and are at least partly related to collateral damage of islets extending from exocrine tissue destruction. CFRD development is not universal and is likely influenced by multiple other factors including inflammation, genetic susceptibility, and nutritional status. The direct role of the CFTR, the transepithelial chloride and bicarbonate ion channel that is defective in CF, in impaired insulin secretion remains unclear. Clinical, animal, and in vitro studies are positioned to further refine our understanding of CFRD development.

5.1 | Pancreatic pathology

Abnormal CFTR function results in thick viscous secretions and obstructive damage to the exocrine pancreas and progressive fibrosis and fatty infiltration. In pancreata from people with CFRD, this fibrosis and fatty infiltration extends to islets where it disrupts and destroys islet architecture and contributes to endocrine β-, α-, and pancreatic polypeptide-cell loss.[23–25] Most PwCF, with or without CFRD, have lost about half of their islet mass. Data suggests β-cell loss is not simply a by-product of exocrine tissue damage but also a manifestation of reduced β-cell progenitor survival, β-cell proliferation, and perhaps β-cell specification of progenitors.[26] Inflammation may also have a role as islets from individuals with CFRD demonstrate immune cell infiltration[27] but preserved insulin and glucagon secretion during isolated islet perifusion[27] while pancreata from both pediatric and adult individuals with CF with and without CFRD demonstrated enhance interleukin-1β staining alongside relatively preserved β-cell area and higher α-cell area.[28]

β-cell destruction is not related to autoimmune disease in CF, since the frequency of diabetes autoantibodies and human leukocyte antigen types associated with T1D are similar to that of the general population.[29,30] However, individuals have occasionally been found to have both T1D and CF.

5.2 | The role of insulin insufficiency

The primary defect in CFRD is insulin insufficiency. Virtually all pancreatic exocrine insufficient individuals, with and without diabetes, show evidence of β-cell dysfunction.[6,31] These insulin secretion

defects are present even in the setting of NGT and manifest as progressive dampening and ultimately complete loss of early-phase insulin secretion (insulin secretion occurring within first 30-min of an OGTT or meal consumption) as glucose tolerance worsens. Fasting insulin secretion is generally preserved.[8,32–35] Insulin secretory defects are found in the earliest years of life[36] and tend to worsen with increasing age.[34] Whether insulin secretory defects also occur in the setting of pancreatic exocrine sufficiency is unclear.[9,37]

5.3 | The role of insulin resistance

In persons without CFRD, insulin sensitivity has generally been reported to be intact; some investigators have found insulin resistance likely related to more severe illness.[38–41] In fact, while most of individuals are insulin sensitive during their baseline state of health, insulin resistance acutely worsens during periods of active infection and may unmask underlying insulin secretion defects and ultimately hyperglycemia.

Individuals with CFRD are modestly insulin resistant, with both decreased peripheral glucose uptake and poor insulin-mediated suppression of hepatic glucose production.[39,40] As with individuals without CFRD, insulin resistance assumes an important role during periods of stress such as acute pulmonary exacerbations and with systemic glucocorticoid therapy, and increases with age.[42]

Additionally, with the advent of HEMT, rates of obesity are increasing[43] which will likely increase insulin resistance in people with CFRD. Please see Section 7.2 for additional details.

5.4 | Genetics of CFRD and HEMT therapy

CFRD is more common in specific (more severe) *CFTR* mutations, leading to speculation of a direct role for *CFTR* in islet function, and hope that HEMT therapy could cure and prevent CFRD.

CFTR RNA may be expressed in a small subpopulation of human islet β-cells,[27,44–46] but immunocytochemistry of human islets did not identify CFTR protein co-expression with insulin-positive, glucagon-positive, or somatostatin-positive cells.[27] Moreover, CFTR modulators and inhibitors did not impact in vitro insulin secretion by human islets.[27] Non-specific inhibition of islet chloride channels by CFTR inhibitors[47] has been suggested to underlie in vitro murine and human islet studies identifying impaired insulin secretion with CFTR inhibition.[48]

CFTR modulators must match the specific *CFTR* mutation and include: ivacaftor (IVA) alone for G551D and other gaiting mutations, lumacaftor/ivacaftor (LUM/IVA), tezacaftor/ivacaftor (TEZ/IVA) and elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) for deltaF508 *CFTR* mutation. Only IVA used in gaiting mutations and ELX/TEZ/IVA are highly effective modulators (HEMT) providing a near cure for PwCF. Unfortunately, it has become clear that HEMT does not resolve established CFRD. Studies to this point have shown IVA is associated with small increases in insulin secretion and markers of beta cell function, but not glucose tolerance.[49,50] A registry study utilizing data from both the United States and the United Kingdom demonstrated a slower increase in prevalence in CFRD with IVA,[51] However, these data are tempered as the comparison group had more severe CFTR genotypes (with higher baseline risk for CFRD) than the IVA group. Many more PwCF are eligible for LUM/IVA, however, only a small uncontrolled study found improved glucose tolerance[52] whereas a similar study showed no improvement.[53] There is even less data on the highly effective modulator ELX/TEZ/IVA but what is available is promising and further studies are ongoing.[49,54]

Shared genetics between CF and T2D has been suggested by the increased prevalence of CFRD in monozygotic versus dizygotic twins with CF,[55] increased prevalence of CFRD in individuals with a family history of T2D,[55] and associations with T2D susceptibility loci including *TCF7L2*, *CDKAL1*, *CDKN2A/B*, and *IGF2BP2*.[55–57] Variants in *SLC26A9*, which encodes an anion transporter recently demonstrated to be co-expressed with CFTR in a subset of pancreatic ductal cells,[44] associate with age at CFRD onset[56,57] but are not known to confer increased T2D risk. Differences in genes associated with inflammation such as tumor necrosis factor[32] and Calpain-10 also appear more common in CFRD.[58] These findings may provide insight into the progressive worsening of insulin secretion defects and glucose intolerance and ultimately interventions aimed at preserving β-cell function.

TABLE 2 Symptoms of CFRD

- Unexplained polyuria or polydipsia
- Failure to gain or maintain weight despite nutritional intervention
- Poor growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function

There may be no symptoms.

6 | CLINICAL FEATURES OF CFRD

Onset of CFRD is typically asymptomatic and gradual with the majority of persons experiencing clinical decline prior to obvious symptoms or classic signs of diabetes.[3,59,60] Symptoms may include polyuria, polydipsia, failure to gain or maintain weight, poor growth velocity and unexplained chronic decline in pulmonary function (see Table 2). DKA is rare and should raise concern for the potential of co-occurring T1D. CFRD may first present during situations where insulin resistance is increased, such as acute pulmonary infection or glucocorticoid therapy, or during high carbohydrate food supplementation such as continuous nighttime enteral tube feedings. Unfortunately, diabetes is common in the setting of lung transplantation, where pretransplant individuals are critically ill and insulin resistant, and posttransplant receive diabetogenic medications such as steroids and calcineurin inhibitors.[61–64] In PwCF on HEMT, and/or with increasing age, signs of insulin resistance have been documented, which may contribute to progression toward frank CFRD.[42] The prevalence of CFRD is higher in individuals with CF-related liver disease.[65]

7 | SURVIVAL AND PROGNOSIS

7.1 | Increased mortality in CFRD

Beginning in the 1980s, the diagnosis of CFRD was associated with increased mortality, particularly in women.[2,66–69] Unlike people with T1D and T2D in whom increased mortality is attributable to macrovascular and microvascular disease, people with CFRD almost always die from pulmonary failure. Diabetes has been directly implicated in CF lung function decline because of both the catabolic effects of insulin insufficiency on nutritional status and muscle mass[59,70–72] and the negative impact of chronic hyperglycemia on lung function.[73–76] A 2009 report examining temporal trends in CFRD mortality in a large, well-defined CF population followed longitudinally at one institution found a significant and steady decline in the risk of death associated with CFRD between 1992 and 2008.[22] This substantial improvement in the mortality associated with CFRD was attributed to annual diabetes screening and early institution of insulin therapy. With overall improvements in the health of PwCF, particularly in the large subset treated with highly effective modulator therapy, the relationships of CFRD with increased mortality related to pulmonary failure will require ongoing surveillance to determine if the risk is further ameliorated. Unfortunately, in the only study so far, use of IVA in G551D mutations did not prevent excess lung function decline from CFRD, indicating HEMT therapy alone may not be sufficient to prevent increased morbidity from CFRD.[77]

7.2 | Microvascular and macrovascular complications

Diabetes microvascular complications occur in CFRD. In Denmark, 36% of PwCF with more than 10 years duration of diabetes had retinopathy.[78] In a US series of 285 CFRD individuals, diabetes complications were rare before 10 years duration of diabetes; thereafter, in those with fasting hyperglycemia, 14% had microalbuminuria, 16% retinopathy, 55% neuropathy, 50% gastropathy.[15] In Wales, 42% (18/43) of people with CFRD who underwent retinal scans had evidence of retinopathy ranging in severity from mild to proliferative retinopathy.[79] CFRD requiring insulin therapy for >5 years substantially increased the risk of chronic kidney disease.[80] Therefore, screening for microvascular complications is recommended annually beginning 5 years after the diagnosis of CFRD.

At the current time, case reports of established cardiovascular disease remain rare.[81–83] Overweight/obesity are increasingly prevalent in adults with CF.[84,85] Blood pressure increases with increasing age in CF.[86] In a US cohort of 484 adults with CF, the prevalence of hypertension was 17% in normal weight CF adults increasing to 31% in overweight adults.[84] Studies of vascular distensibility suggest subtle changes, traditionally recognized as precursors to cardiovascular complications in non-CF populations, may be present in CF.[87,88] Prior to the introduction of HEMT, cholesterol has been generally low in CF.[89–92] Although a recent study of 256 Canadian adults with CF found hyperlipidemia in a small percentage, it was not associated with CFRD or hyperglycemia.[42] A separate large Canadian study found weight gain was associated with better pulmonary function but increased insulin resistance and dyslipidaemia.[93] Similar findings have also been seen in smaller studies in US adults.[94] With the changing demographics, nutritional status, and overall health of people with CF, cardiovascular disease risk in CF may need to be reconsidered.

7.3 | Increased morbidity in the prediabetes state

Several studies have shown an insidious decline in clinical status in the years before the diagnosis of CFRD, during the insulin-insufficient, prediabetic state.[3,38,59,60,66] In a prospective study, the decline in pulmonary function over 4 years was least in individuals with NGT, greater in persons with IGT, and greatest in PwCF with untreated early diabetes.[3] In this study and others,[34] pulmonary deterioration correlated with the severity of insulin insufficiency. More contemporary data from the US CF Registry (2008–2015) identifying greater declines in pulmonary function in the 2 years prior to CFRD diagnosis in CF Centers with lower screening rates[95] continue to suggest delayed diagnoses contributes to worse outcomes. Recently, isolated elevations in the 1-h OGTT glucose and higher glucose excursions identified with CGM were weakly related to pulmonary function.[96,97]

Because protein catabolism, malnutrition, and death are associated in CF and because insulin is a potent anabolic hormone, insulin insufficiency has been considered of greater consequence in CF than the traditional metabolic impact of hyperglycemia. The catabolic effect of insulin insufficiency may be most important in growing children.[98–100] With the emergence of overweight/obesity[84,101] and better overall health in people with CF, particularly with HEMT,[102] insulin insufficiency may pose less of a threat to nutritional status and pulmonary function.

8 | HYPOGLYCEMIA

As in other forms of diabetes, hypoglycemia can be a complication of CFRD treatment. Spontaneous hypoglycemia is also experienced by PwCF who do not have diabetes and are not on glucose-lowering therapies. Hypoglycemia is usually described as reactive, occurring during or after an OGTT (with a prevalence ranging from 7% to 60%),[34,103,104] as well as during the post-prandial state and in the fasting state of PwCF with suboptimal clinical status.[34] Hypoglycemia in these contexts in CF is generally self-limited and is rarely symptomatic even when BGLs are severely reduced, which raises concerns of under recognition and potential hypoglycemia unawareness.[105,106]

Multiple mechanisms may lead to hypoglycemia in CF. Studies have shown that the glucagon counterregulatory response is impaired and only in part compensated by an intact or attenuated catecholamine response.[8,104,105] The timing of insulin secretion is generally delayed, leading to inappropriately high insulin secretion during the descending phase of BGLs of a glucose challenge.[8,104] Furthermore,

PwCF with more severe insulin secretory defects may be at higher risk of hypoglycemia.[105]

As with all individuals on insulin therapy, hypoglycemia is a risk that PwCFRD and their families must know how to anticipate, prevent, and treat. In a few individuals with CFRD, therapy with modulators has dramatically improved their glycemic management leading to ongoing recurrent hypoglycemic events off insulin therapy.[107] This phenomenon will need ongoing research.

For PwCF, hypoglycemia may be a concern also in the absence of diabetes and related therapy. Therefore, PwCF should be queried for symptoms of post-prandial hypoglycemia. After the conclusion of an OGTT their BGLs should be monitored, and they should be advised to eat following the test. Interestingly, those who experienced hypoglycemia during OGTT appear to have lower rates of progression to IGT and CFRD[108,109] However, the potential risks of repeated hypoglycemia and hypoglycemia unawareness are presently unknown in these individuals.

9 | SCREENING FOR CFRD

Because CFRD can be associated with an increased risk of clinical decline (e.g., accelerated weight and/or lung function loss) but often may be clinically silent,[3,59,60,66,110] routine screening is important.[95] The standard OGTT (after an 8 h fast, 1.75 g/kg body weight oral glucose up to a maximum of 75 g, 2 h test) is at present the recommended screening test. Screening is recommended annually starting at age 10 years, and it is also recommended in situations where individuals are at higher risk for hyperglycemia (e.g., steroid initiation, pregnancy, enteral or parenteral nutrition support, etc.)

9.1 | Oral glucose tolerance test

The North American CFRD Guidelines Committee determined that the OGTT is the screening test of choice for CFRD.[5] This recommendation is based on: (1) the poor performance of other tests in CF relative to the OGTT (e.g., fasting BGL, A1c); (2) the availability of long-term prognostic data linking OGTT results to relevant clinical outcomes such as an increased risk of weight and/or lung function decline[3,6,30]; (3) improvements in nutritional status and pulmonary function observed with insulin therapy[111–113]; and (4) the importance of diagnosing CFRD early to reduce the risk of CF-specific outcomes as well as diabetes-related microvascular complications (e.g., retinopathy).[15,114]

A diagnosis of CFRD is based on elevated fasting and/or 2-h BGLs. These values also serve to identify prediabetes categories: IFG, IGT, and indeterminate glycemia (see Table 1). These prediabetes categories are associated with increased risk of developing CFRD[115] and may also identify individuals at higher risk for weight and lung function decline.[3,6,116,117]

It is recommended that OGTT screening begin by at least 10 years of age. While overt diabetes is rare before 10 years of age, 42% to 78% of children with CF ages 9 years and under are reported to have abnormal glucose tolerance.[118,119] A retrospective study at one North American CF center found that in children ages 6 to 9 years, IGT or indeterminate glycemia each predicted a high risk of progression to diabetes in the early adolescent years.[118] For this reason, some centers and associations choose to begin screening at 6 years of age.[120]

9.2 | Prediabetes categories: IFG, IGT, and mid-OGTT glucose elevations

The North American CFRD Consensus Conference in 2009 defined glucose tolerance in individuals with a 1 h BG (BG1) > 11.1 mmol/L (200 mg/dl) as indeterminate (INDET) glycemia. There is some evidence that mid-OGTT glucose elevations may be predictive of CFRD[16,93,115,121–123] and pulmonary function and weight decline.[124–127] Thus, consideration should be given to measuring intermediate glucose levels during the 2-h test.[115,124,125] In a large study of more than 1000 German and Austrian PwCF over 10 years of age, IFG, IGT, and INDET were all predictors of future CFRD.[115] Similarly, a US pediatric study found that youth with a INDET were 10 times more likely to develop CFRD over the subsequent 5 years.[123] The combined presence of both IGT and INDET also appears to identify a unique group at higher risk for CFRD.[115,128]

Lower BGL1 thresholds of >8.6 mmol/L (155 mg/dl) and even > 8 mmol/L (>140 mg/dL) have been proposed to identify those with greater ß-cell dysfunction, risk of CFRD, and clinical decline.[16,123,124,129] However, these associations have not been consistently demonstrated across studies.[123,129–131] At least one recent publication suggests that such associations may be less evident for adults with CF in the context of modern CF-treatments,[130] and additional research is necessary before these measures can be used to guide clinical interventions.

Adherence to screening recommendations for an annual OGTT also continues to be a challenge across CF centers, with fewer than 50% of eligible adults with CF undergoing routine screening at adult centers in North America.[21,132] This could have adverse consequences as individuals followed in centers with low screening rates have faster rates of pulmonary decline prior to CFRD diagnosis.[95] Barriers to screening include fasting and multiple sampling times, as well as lack of understanding surrounding the implications of testing. Furthermore, given the variability of OGTTs, particularly in this population,[17] repeat testing is recommended to confirm a diagnosis of CFRD.[5,13] The resultant burden of testing has led to attempts to shorten this test with intermediate OGTT glucose measurements.[133] Others have proposed to reduce the number of required OGTTs with a stepwise approach using either HbA1c,[134] random BGL,[135] or a first step 1 h glucose challenge test[136] or other intermediate OGTT BGs.[93] However, larger prospective studies are needed before these can be recommended, particularly in the highly effective modulator era, in order to inform evidence-based recommendations.

9.3 | HbA1c for screening and diagnosis

HbA1c is unreliable in the diagnosis of CFRD because it has low sensitivity for identifying CFRD detected by OGTT[6,11,137,138] and poor

ability to differentiate among different glucose tolerance categories.[139] When using ADA criteria for diagnosing diabetes with an HbA1c cut point of 48 mmol/mol (6.5%), many individuals with early CFRD defined by OGTT will be missed.[110,140] Historically, HbA1c has been thought to underestimate glycemia in CF, and this has been postulated to be due to increased red blood cell turnover related to chronic inflammation.[141] More recent reports from youth and adults with CF suggest that HbA1c has a similar relationship to mean glucose as described in other populations with diabetes.[7,142] As a measure of average glycemia over the preceding 2–3 months, HbA1c rises when average BGLs increase, but this test may miss individuals with normal fasting and average glucose concentrations but who have postprandial glucose excursions that are better captured by an OGTT. Thus, an elevated HbA1c is evidence of hyperglycemia, but a normal HbA1c does not exclude it.

Increasingly, studies are investigating alternate, lower HbA1c thresholds that may aid CFRD screening. In retrospective studies from pediatric and adult individuals with CF, an HbA1c value below 5.5% to 5.8% (37–40 mmol/mol) was associated with a low risk of developing CFRD.[132,137,143,144] A stepwise approach using HbA1c as a first line screening tool, for example, could reduce the number of required OGTTs.[134] However, variability in HbA1c assays still exist and additional studies are needed to validate a specific HbA1c cutpoint that would decrease the burden of OGTTs without missing cases of CFRD.

Other measures of average glycemia, including fructosamine, 1,5-anhydroglucitol, and glycated albumin, have been investigated in small studies in the CF population, but thresholds have not been identified that outperform HbA1c or OGTTs at identifying those at risk for CFRD.[137,145]

9.4 | Random and fasting BGLs, or SMBG for CFRD diagnosis

Normal fasting or random BGLs do not exclude a diagnosis of CFRD, as nearly two-thirds of individuals with de novo CFRD do not have fasting hyperglycemia.[22] However, in some high-risk situations such as hospital admissions for pulmonary exacerbations or need for intravenous antibiotics or initiation of gastrostomy feedings, it is practical to perform initial prescreening with bedside glucose checks or home monitoring with SMBG (see Special circumstances Section 9.6). SMBG is not sufficiently accurate to make a diagnosis of CFRD, and subsequent laboratory screening must occur in individuals identified as high-risk by SMBG.

9.5 | Continuous glucose monitoring

CGM has been validated in people with CF and is generally accepted to be useful for glucose monitoring in individuals with insulin-treated CFRD, where it can help guide safe and effective insulin therapy.[12] Its role in PwCF who do not have diabetes and/or to establish a diagnosis of CFRD is less clear. Glucose abnormalities captured by CGM are common in CF, including in very young children[96,146]; however, there are as yet neither established criteria using CGM for screening nor diagnosing diabetes.[121,142] Retrospective and cross-sectional single-center studies have associated glucose abnormalities on CGM with ß-cell dysfunction on OGTT,[121] weight decline,[125] lower lung function,[96,147] and elevated inflammatory markers.[148] However, evidence from larger multi-center studies are lacking to support the benefits of treating intermittent elevations in blood glucose concentrations prior to a diagnosis of diabetes. For now, CGM should be considered a useful tool for insulin dosage adjustment and to alert individuals to hypoglycemia, however, additional studies are needed before CGM criteria can be used for screening or diagnosis of CFRD or for identifying individuals at higher risk of pulmonary function and weight decline.

9.6 | Situations associated with an increased risk for new onset CFRD

Gestational diabetes can develop earlier in pregnancy in PwCF compared to those at risk for T2DM with prevalence rates ranging from 11% to 36%.[19,149,150] OGTT screening for preexisting diabetes should be done before or immediately after the onset of pregnancy, and screening for gestational diabetes is recommended at the end of both the first and second trimesters.[5]

Additional high-risk situations in which increased glucose monitoring (by SMBG and/or CGM) is recommended include pulmonary exacerbations requiring hospital admissions for intravenous antibiotics, initiation of gastrostomy tube feedings, use of systemic glucocorticoids, and organ transplantation. Recommendations are to monitor fasting and 2-h post-prandial glucose levels for the first 48 h of hospitalization. A diagnosis of CFRD is confirmed when fasting BG ≥126 mg/dl (≥7 mmol/L) or 2-h postprandial BG ≥200 mg/dl (11.1 mmol/L) are detected and persist for at least 48 h, with 2 or more elevated BGL values. PwCF on enteral feeds should be screened with mid- and immediate post-feeding BGLs at the time of initiation of gastrostomy tube feedings and then monthly. CFRD is diagnosed when mid- or post-feeding BGLs are ≥200 mg/dl (11.1 mmol/L) on 2 separate days. Given the importance of maintaining glucose values in target range for transplant outcomes, CFRD screening with an OGTT is recommended in the 6 months prior to transplant.[5] Post-transplant, immediate close bedside BGL monitoring is important, particularly given the increased risk of diabetes with glucocorticoids and other immunosuppressive agents.[151,152] It is recommended to verify elevations captured by SMBG with plasma glucose measurements.

9.7 | Additional scenarios

Pancreatic sufficient CF

Individuals with PS are at lower risk for development of CFRD than those with PI.[153] The presence of exocrine defects have been shown to increase risk for insulin secretory defects[8,37] and therefore

TABLE 3 Dietary recommendations for CFRD[a]

Calories	Standard requirements are 120%–150% of normal caloric intake for age and gender to prevent underweight[a]
Fat	40% of total energy
Total carbohydrate	45%–50% total energy
Protein	200% of reference intake for a non-CF individual
Salt	Increased requirement: unrestricted intake

Note: See ISPAD 2022 Consensus Guidelines Chapter 10 on Nutritional Management in Children and Adolescents with Diabetes.
Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis related diabetes; HEMT, highly effective CFTR modulator therapy.
[a]This recommendation may change in individuals on HEMT given increasing overweight in that population.

CFRD. Given this low risk, particularly with a normal 2-h glucose, it would be reasonable for PS individuals with normal glucose tolerance to reduce frequency of OGTT screening to every 3–5 years.

Evaluation for Type 1 Diabetes

Individuals with CF can also develop T1D with a similar risk as seen in the general population.[154] Therefore, screening for T1D with islet autoantibodies is recommended in scenarios where individuals may present with risk factors for T1D, including: new onset diabetes <10 years of age, co-existence of autoimmune diseases or family history of autoimmunity in first degree relatives, higher insulin needs at onset,[155] development of DKA, or presence of ketones.

Future of CFRD screening and impact of CFTR modulators

The effects of CFTR modulator therapy on the incidence and prevalence of CFRD remain uncertain. Registry studies from the United Kingdom and United States 5 years after the introduction of ivacaftor have suggested a lower prevalence of CFRD relative to those untreated with CFTR modulators.[51] However, CFTR modulators are also increasing weight and BMI,[102] which may also increase risk for insulin resistance. With the recent introduction of triple-combination-therapy CFTR modulators to the wider CF population, prospective studies are needed to determine the longer-term implications on the epidemiology of CFRD.

10 | TREATMENT OF CFRD

10.1 | Medical nutritional therapy

The dietary recommendations for persons with CFRD are very different from those for persons with T1D or T2D (Table 3), both because their needs are very different, and because they are at low risk for cardiovascular disease.[156] PwCF, including those with CFRD, require a high-calorie, high-salt, and high-fat diet. Caloric restriction is almost never appropriate (although it may be considered in older individuals with milder CF mutations who are overweight, and in the currently uncommon, but emerging, group of PwCF who are obese). For individuals on multiple-daily injections or insulin pump therapy, carbohydrate counting is useful for determining the premeal insulin dose. Sugar-sweetened beverages are generally discouraged. Although some people with CFRD do utilize this,[157] nutritional management alone (without insulin/medical treatment) is not recommended.

10.2 | Insulin therapy

Insulin insufficiency is the primary pathologic feature of CFRD, and therefore insulin replacement is the recommended medical treatment.[5]

Insulin therapy stabilizes lung function and improves nutritional status in persons with CFRD.[22,158] The general principles of insulin therapy are presented in Table 4. When these individuals are in their baseline state of health, insulin requirements tend to be modest because of the persistence of endogenous insulin secretion (average insulin dose of <0.5–0.8 units/kg/d in both adolescents and adults).[114,159] When insulin secretion declines, they may eventually develop fasting hyperglycemia, and are generally treated with basal-bolus therapy with an insulin pump or with a combination of long-acting basal insulin and rapid-acting insulin. In persons with CFRD without fasting hyperglycemia, premeal rapid-acting insulin was demonstrated in the CFRDT trial to reverse chronic weight loss and is now considered standard care.[22] Some young people (especially those that consume modest amounts of carbohydrates multiple times during the day) may be successfully treated with basal insulin therapy alone.

Advanced diabetes technology

Insulin pumps provide continuous subcutaneous infusion of rapid- or short-acting insulin. They can be utilized without CGM or combined with CGM either in an open loop (the individual enters the glucose values into the pump), partial closed loop (a pump algorithm increases and decreases insulin autonomously in some circumstances) or hybrid closed loop (the algorithm nearly fully controls insulin dosage with minimal user input). These devices have revolutionized care for children, youth, and adults with T1D. For further details see the ISPAD 2022 Consensus Guideline Chapter 16 on Diabetes Technologies: Insulin Delivery.

Insulin pump therapy without CGM has been associated with improved glycemic management and lean body mass in small studies, mostly secondary to better coverage of meals and snacks in people with CFRD.[160] A small study of teens and adults with CFRD found that transition from open loop with CGM to partial closed loop was associated with increase percent time in target range without increase in hypoglycemia.[49] In a pilot study investigating a closed loop device in 3 individuals with CFRD there were non-significant improvement in mean glucose (likely due to small size) but significant improvements in treatment satisfaction and decreased treatment burden.[161] However, there is a study in progress to further evaluate the use of closed loop insulin pump therapy (clinicaltrials.gov/ct2/show/NCT03258853). While there is not the degree of evidence for use of these devices in CFRD as there is in T1D, the existing data indicate that there is likely real benefit to utilization of advanced diabetes technology where available.

Lower cost regimens

Combined Neutral protamine Hagedorn (NPH) and regular insulin regimens have been used with success in CFRD. The major disadvantage is that NPH regular regimens are inflexible which is problematic for

TABLE 4 Principles of insulin therapy in CFRD

General principles	• CFRD persons typically require 0.5 to 0.8 units insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress, illness, times of systemic glucocorticoid use, or puberty. • Because of the catabolic effects of insulin insufficiency, the goal is to give the person as much insulin as can be safely tolerated without hypoglycemia. • Choose the insulin regimen that best fits the individual's lifestyle and meets the needs of their CF management.
Basal insulin	• Generally, the goal is about 0.25 U per kg body weight per 24 h; start at half this and adjust upward based on fasting glucose levels.
Meal coverage	• A common starting dose is 0.5 to 1 U rapid-acting insulin for every 15 g of carbohydrate consumed. Insulin pens or syringes that deliver half units may be needed. • The dose is adjusted by increments of 0.5 U per 15 g carbohydrate to achieve 2-h postprandial BGL goals. • For very young people or those who are unsure of what they will eat due to nausea or gastroparesis, the dose may need to be given right after the meal (although before is always better, if possible, in order to reduce hyperglycemia following the meal). • Persons with CFRD without fasting hyperglycemia may be managed with premeal insulin alone, or with basal alone, or both (depending on individual factors, including eating habits)
Correction dose (sensitivity)	• Premeal correction is usually started at 0.5 to 1 U rapid-acting insulin for every 2.8 mmol/L (50 mg/dl) above 8.3 mmol/L (150 mg/dl) and adjusted as needed.
Coverage of overnight drip feeding	• Overnight enteral (drip) feeds: 8-h feeds can be treated with a combination of a single dose of regular/soluble insulin (or rapid-acting/analog insulin) plus the intermediate insulin Neutral Protamine Hagedorn (NPH) or Detemir. The regular insulin covers the first half and the NPH the second half of the feeding; 12 h feeds can be covered with insulin detemir. • Starting dose: calculate the total grams carbohydrate in the feeding, determine a total insulin dose based on the insulin to carbohydrate ratio (typically 0.5–1 units per 15 g) and deliver half of this as regular and half as NPH insulin for an 8 h feed or 100% of the dose as detemir for a 12 h feed. • BGLs 4 h into the feeding are used to adjust the regular insulin dose and those at the end of the feeding to adjust the NPH insulin dose. If using detemir, BGL at the end of the feed is used to adjust insulin dosing. Occasionally a little rapid-acting insulin is also needed at the beginning for correction. • Think of this as a "long meal." It does not replace basal insulin, and individuals should only take this insulin when they have the overnight feeding.
Limited care in a resource-poor setting	• When analog insulin is not available, NPH (isophane) insulin and regular/soluble insulin can be used to treat CFRD, but care needs to be taken to avoid late postprandial hypoglycemia. One possible regimen is NPH insulin at bedtime, and regular insulin with breakfast, lunch, and supper, in an individual who is eating three meals and three snacks a day. • When using and NPH/regular insulin for MDI 2/3 of the total daily dose (TDD) is given in the morning, with 2/3 of that being NPH and 1/3 regular insulin. The other 1/3 of the TDD is administered in the evening, half as NPH and half as regular. TDD is calculated as listed in general principles above. NPH lasts for 8 h and has a marked peak at 4 h. Therefore, an individual who is treated with NPH must eat lunch and must eat an appropriate bedtime snack, or they are at significant risk for severe hypoglycemia. • There is often limited availability of BG monitoring test strips in resource-poor settings. The goal is to test as often as possible, varying the time from fasting to 2 h postprandial readings, to try to get a representative sample of how well the insulin doses are working.

Abbreviations: CF, cystic fibrosis; CFRD cystic fibrosis related diabetes; NPH, neutral protamine hagedorn insulin.

PwCF who commonly have variable appetites. There has been one small study done in PwCFRD comparing a single dose of NPH to a single dose of glargine insulin in a crossover study in 19 subjects which found greater weight gain and reduction in fasting BG levels with glargine.[162] It is important to maintain adequate nutrition support even when unable to access diabetes specific treatments, and diet should not be restricted in an attempt to treat hyperglycemia. CF-specific nutritional guidelines should be followed as much as possible, although it is reasonable to limit high simple sugar foods with low nutritional value.

10.3 | Non-insulin treatments

Guidelines have not yet recommended oral diabetes agents for the treatment of CFRD. This is not only due to the importance of insulin in CFRD but also inadequate data to recommend the use of other diabetes therapeutics,[163] and concerns regarding side effects. New data may support use of non-insulin medications in well-defined circumstances.[164,165] However, there are only a limited number of studies in the area to guide clinical practice.

The CFRDT trial[22] randomized adult PwCF with IGT or CFRD without fasting hyperglycemia to multiple daily injections of pre-meal insulin aspart, the oral insulin secretagogue repaglinide, or oral placebo. BMI remained suboptimal in the placebo arm, temporarily increased in the repaglinide arm, and showed sustained increase in the insulin arm. Somewhat conversely, results of a more recent multicenter European study[164] (comparing multiple daily injections of regular insulin and repaglinide in both children and adults with CF) found no difference in HbA1c, BMI, lung function, or adverse events after 2 years.[164] These results should be interpreted with caution.[166] In

both RCTs[111,164] the drop-out rate was high (around 20% at 12 months), the insulin dose was not reported[111] or variable[164] and outcomes of the insulin-treated arms may have been adversely affected by inadequate dosing and suboptimal usage of insulin. A recent Cochrane review concluded that there was not yet conclusive evidence that any agent has a distinct advantage over another therapy in CFRD at present.[165]

However, there are plausible theoretical concerns with non-insulin therapies. It is possible that insulin secretagogues could accelerate the loss of ß-cells if they are already under stress.[167] Agents that reduce insulin resistance are unlikely to be effective in CFRD, because insulin resistance is not the primary etiology of CFRD, although this could potentially change if obesity rates continue to increase with HEMT therapy. Furthermore, currently available insulin sensitizers might be particularly unacceptable in the CF population, due to gastrointestinal side effects (metformin) and osteoporosis (thiazolidinediones), for which PwCF are already at increased risk. There are ongoing studies (NCT01851694) of incretin mimetic agents such as the glucagon-like peptide-1 (GLP-1) agonists or the dipeptidyl peptidase-4 (dpp-4) inhibitors, and small studies show GLP-1 agonists increased insulin secretion in PwCF with glucose intolerance.[168] However, an RCT on the effect of Sitagliptin (a DPP-IV inhibitor) on islet function in pancreatic insufficient PwCF with abnormal glucose tolerance found no improvement in meal-related glucose excursion or insulin response.[169]

10.4 | Treatment of PwCF with abnormal glucose tolerance

Small, uncontrolled studies suggest that individuals with IGT might benefit from insulin therapy.[158,170–172] However, there are no definitive data on the benefits of insulin therapy for PwCF without a diagnosis of diabetes. This has been identified as a high-priority research question,[5] and two large studies in the United States and Australia ("CF-IDEA Trial" clinicaltrials.gov: NCT01100892 and "The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients" clinicaltrials.gov: NCT02496780) are in progress to address this issue (Data S1).

There are also small, uncontrolled studies/case reports reporting the effect of the oral insulin secretagogue tolbutamide in CF children with normal glucose tolerance[173] showing improved glucose homeostasis, linear growth and lean body mass, and the sulfonylurea glipizide,[174] showed improved A1C and reduced urinary glucose but no change in BMI.

11 | QUALITY OF LIFE AND PERSPECTIVE OF PEOPLE WITH CF

A diagnosis of CFRD complicates the medical management of an already complex condition by increasing treatment demands, and for individuals with markedly improved lung function due to HEMT may become their primary chronic illness to manage.

The literature reports inconsistent effects of CFRD on HRQoL. A study by Tierney et al (2008) found no difference in HRQoL due to hypoglycemia in CFRD compared to T1D despite similar rates of hypoglycemia.[175] Similarly Havermans et al.[176] found no association between CFRD and treatment burden and Dill et al. found CFRD not to be a significant predictor of HRQoL.[177] Conversely, Kwong et al. identified a significant negative association between different glycemic patterns and treatment burden, with worsening glycemia being associated with increased treatment burden.[178] Additionally, Abbott et al.[179] followed 234 participants aged 14–48 years over a 12-year period and found that a CFRD diagnosis was important for more than half of the HRQoL domains. Additional large-scale longitudinal studies are needed to further assess the added effect of a second chronic disease on mental health in these individuals and the burden of management and quality of life. Nonetheless, providers should remain cognizant of potential negative effects of the diagnosis on the overall well-being of individuals with CFRD.

AUTHOR CONTRIBUTIONS

All authors reviewed and summarized literature regarding CFRD and drafted one or more sections of the manuscript. All authors reviewed and edited the manuscript drafts. KLO coordinated revisions of the manuscript based on input form the co-authors and reviewers.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ode KL, Ballman M, Battezzati A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1212-1228. doi:10.1111/pedi.13453

Received: 12 September 2022 | Accepted: 16 September 2022

DOI: 10.1111/pedi.13418

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes education in children and adolescents

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1 | SUMMARY OF WHAT IS NEW OR DIFFERENT

This chapter has been updated with additional details and references on educational approaches for multidisciplinary teams, including cultural adaptation, as well as a section on type 2 diabetes (T2D) in youth. Diabetes education and digital technologies as well as telemedicine, with increased adoption of video or phone appointments, has also been expanded and enhanced.

2 | RECOMMENDATIONS/EXECUTIVE SUMMARY

Education is the key to successful management of diabetes [E].

- To maximize the effectiveness of diabetes treatment and the advances in diabetes management and technology, including continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM), it is advisable that quality assured structured education is available to all young people with diabetes and their caregivers [E].
- The content, curricula and delivery of structured education needs regular review to ensure it suits the needs of people with diabetes within the community, matches local practice, changes with the changing maturity, and needs of the child and then adolescent; and reflects contemporary diabetes management methodologies and technology [E].
- Evaluation of structured educational programs should include a measurement of outcomes directly related to diabetes education such as the individual's achievement of self-selected diabetes care

goals; improved psychosocial adaptation; quality of life and enhanced self-efficacy, in addition to measures of glycemic control. Adequacy of glycemic control should encompass not only HbA1c, but other measures such as time in range, if available, and frequency of hypoglycemia [E].

- Educational interventions have a beneficial effect on glycemic and psychosocial outcomes in children and adolescents with diabetes [E].
- Educational interventions shown to be effective include those:
- Based on clear theoretical psychoeducational principles [E].
- Integrated into routine clinical care (e.g., as an essential and integral part of care at diabetes onset and ongoing) [A].
- Part of an ongoing process to provide education in individualized self-management and psychosocial support [E].
- Involve the continuing responsibility of parents and other caregivers throughout adolescence [B].
- Making use of cognitive behavioral techniques most often related to problem solving, goal setting, communication skills, motivational interviewing, family conflict resolution, coping skills, and stress management [A].
- Utilize new technologies in diabetes care as one of the vehicles for educational motivation [A].
- Health care professionals require appropriate specialized training in the principles and practice of teaching and education to implement successfully person-centered behavioral approaches to education, designed to empower young people and caregivers in promoting self-management [E].
- A multidisciplinary education team sharing the same philosophy and goals and speaking with "one voice" has beneficial effects on glycemic and psychosocial outcomes [B].
- It is important that goals and targets for blood glucose and HbA1c align with recommended international guidelines. A major task during the first weeks and ongoing after diagnosis of diabetes is to get the family to agree to pursue the same targets [E].
- Telemedicine, which encompasses the use of video or phone appointments, between a person seeking care and the health care professional, offers an important alternative to in-person diabetes review for people who live in remote areas without access to professional counseling and diabetes education resources locally, as well as for routine diabetes care [B].
- Advancements in technology, combined with widespread adoption of digital devices by people with diabetes and the diabetes team, have created an opportunity to leverage digital platforms to augment diabetes care [E].
- Mobile and web-based applications are useful tools for diabetes self-management education to improve diabetes management [E].
- Interactive web-based educational resources are widely used for device-specific training and education of people with diabetes [E].
- Diabetes peers and/or diabetes youth leaders can reinforce the principles of living well with diabetes and support the learning of families, especially those living in remote or resource limited settings [E].

3 | INTRODUCTION

To maintain quality diabetes management, families perform a multitude of self-management tasks daily, responding to changes in activity, food, and physiology. The challenge for diabetes health care professionals is to deliver diabetes education that optimizes the family's knowledge and understanding of the condition and its treatment, while simultaneously assisting them to adjust to the impact of diabetes management on their everyday lives. In addition, parents need to combine managing their child's diabetes-related tasks alongside their usual parenting responsibilities. This challenge is even greater in low- and middle-income countries where limited resources may threaten access to insulin, food security, and the availability of the basic tools to manage diabetes such as glucose and ketone monitoring equipment. Diabetes education is a critical element of diabetes care, regardless of the intensity of the insulin regimen adopted. Diabetes management requires frequent and high levels of educational involvement at diagnosis and ongoing to support the children and adolescents as well as parents and other care givers.[1,2] This evidence informed guideline has been adapted and updated with the aim to describe universal educational principles, details regarding content, and organization of diabetes education in children and adolescents and provide consensus recommendations.[3] Many countries have developed their own set of guidelines, appropriate for their health services and cultural backgrounds.[4–13]

4 | DIABETES EDUCATION—DEFINITION AND UNIVERSAL PRINCIPLES

4.1 | Definition

A universal definition of diabetes education does not exist. However, the following definition has been proposed:

> *"Diabetes education is an interactive process that facilitates and supports the individual and/or their families, caregivers or significant social contacts to acquire and apply the knowledge, confidence, practical, problem-solving and coping skills, needed to manage their life with diabetes to achieve the best possible outcomes within their own unique circumstances."*[14]

4.2 | Empowerment and person-centered care

Regardless of insulin regimen used, the complexity of diabetes treatment requires that children with diabetes and their caregivers make numerous daily treatment decisions, necessitating empowerment of the child or adolescent and their caregivers. Empowerment in health care is defined as a motivational approach to assist people to make health-promoting behavior choices and/or changes.[15] In the field of

diabetes, empowerment is defined as the process of helping people discover and use their innate ability to gain mastery over their diabetes.[16] The approach is person-centered with the health care providers facilitating and providing information and knowledge to assist people in making informed decisions. Persons with diabetes should be empowered to know that they ultimately influence their own lives in making informed decisions about their diabetes. Children and adolescents with diabetes need to have age-appropriate understanding of diabetes and be empowered to participate in the management of their diabetes.[4–7,16,17]

4.3 | Accessibility

Every young person with diabetes should have access to comprehensive structured education to help empower them and their families to manage their diabetes in an age-appropriate manner.[4,6,9–13,18] In addition to the child or adolescent and their primary caregivers, other care providers should have access to educational resources and staff and be included in the educational process.[8,19] Caregivers in nurseries or kindergarten and school teachers should have access to appropriate structured diabetes education.[20–22]

4.4 | Personalized education

Educational programs should utilize appropriate person-centered, interactive teaching methods for all people involved in the management of diabetes. This approach must center around the child or adolescent with diabetes,[4–8,11–13,18] and be adaptable to meet the different needs, personal choices, individualized learning styles of young people with diabetes and their parents, in the context of local models of care. Diabetes education needs to be personalized to the individual's age, stage of diabetes, maturity and lifestyle, culture and learning pace.[4,6,11,12] The sharing of roles and responsibilities for the diabetes treatment tasks between the child or adolescent and their caregivers should be continuously clarified and considered in relation to the need for education.[23,24] This personalized diabetes educational approach remains an integral part of the psychosocial support for young people with diabetes and their families.

4.5 | Multidisciplinary team

Diabetes education should be delivered by a multidisciplinary team of health care professionals who have a clear understanding of the special and changing needs of young people and their families as they transition through the different stages of life.[4,7,8,11,25] Multidisciplinary teams providing education should include, at a minimum, a pediatric endocrinologist/diabetologist or a physician trained in the care of children and adolescents with diabetes, a diabetes specialist nurse/diabetes educator/pediatric nurse, and a dietitian. Furthermore, a psychologist, a social worker or a team member trained in mental health are recognized as essential members of the multidisciplinary team.[6] In areas with limited resources, it is not always possible to have all members of a multidisciplinary team and additional details are provided in the chapter "Limited Care Guidance" (2022 Consensus Guidelines Chapter 25 on Management of diabetes in children and adolescents in limited resource settings).

4.6 | Education of the educators

Educators in the multidisciplinary team must take responsibility for maintenance of their professional development to remain up to date with their knowledge and skills. They should have access to continuing specialized training in current principles of insulin therapy, new diabetes technologies, advances in diabetes education, and educational methods as well as client engagement.[4,6,8,11,12,26,27]

4.7 | Cultural adaptation

Cultural adaptation has been described as the modification of educational approaches to consider language, culture, and context in such a way that it is compatible with the client's cultural patterns, meaning, and values.[28] Due to increased mobility and migration, cultural and language differences may hinder communication and diabetes education. It is recommended that diabetes education is provided with professional translator services if appropriate, and educational material is offered in the family's native language where available.[29]

4.8 | Ongoing engagement

Diabetes education needs to be a continuous process and be repeated on a regular basis for it to be effective.[4–8,11,12] The priorities for health care professionals in diabetes education may not match those of the child and the family. Thus, diabetes education should be based on a thorough assessment of the person's attitudes, beliefs, learning style, learning ability, readiness to learn, existing evidence, knowledge, and goals.[30]

Table 1 summarizes the philosophy of diabetes education in children, adolescents, and their parents.[4,8,31,32]

The knowledge base for some key universal principles is explained in the following sections.

5 | PROVIDING DIABETES EDUCATION

5.1 | Diabetes education and the diabetes health care service

All members of the multidisciplinary diabetes team take part in delivering diabetes education. In the initial phase this will encompass key

TABLE 1 Principles and practice of education in children, adolescents, and their parents/primary care givers

1. Motivation	• The learner needs to and/or have a desire to learn
2. Context	• Where is the learner now? • Where does the learner want to be later?
3. Environment	• Learner-centered, comfortable, trusting • Enjoyable/entertaining/interesting/"open"
4. Significance	• Meaningful, important, links, or joins up • Reward or gain
5. Concepts	• Simple to complex in gentle steps (*short attention span*)
6. Activity	• Constantly interactive • Practical (*fitting into real life*) • Goal setting and problem solving
7. Reinforcement	• Repetition, review, summarize
8. Reassess, evaluate, audit	
9. Move forward (*continuing education*)	

messages that include; (1) informing young people and their families that they have developed diabetes; (2) initiating diabetes education to explain and/or answer the many questions that arise immediately after receiving the diagnosis; (3) informing the child, adolescent, and their primary caregivers about current "best practices" for the management of diabetes; (4) information about how the young person, their family and support network can promote self-management of their diabetes after initial education and instruction.

To maximize the impact of education, a diabetes health care service must formally design what they need to teach and what the young person and family need to learn. A diabetes health care service for young people needs to develop their own, culturally appropriate:

Diabetes education curriculum: a detailed list of contents or subjects to be taught by the health professional and learnt by the young people with diabetes and their families.

Diabetes education syllabus: instructions on the delivery, depth of learning and learning outcomes, considering the needs of the person with diabetes, with content of different subjects and methods. Learning outcomes are "statements that describe the knowledge or skills students should acquire by the end of a particular assignment, class, course, or program, and help students understand why that knowledge and those skills will be useful to them."[33]

National and regional programs[9–12] can and often are adopted by local health services, with sharing of educational resources from other centers, reliable external sources, diabetes support group organizations, and medical societies.

Each Multidisciplinary Diabetes Team needs to construct its own approach to their diabetes education program, based on their health professional numbers, the scope of their health provision resources and social structure of their health environment (Table 2). A check-list approach has been adopted at most diabetes centers, allowing aspects of the education program to be introduced at a manageable pace for the person with diabetes and with allocation of certain learning tasks to different members of the multidisciplinary team based upon their individual expertise.

A completed checklist does not necessarily mean that the young person with diabetes and the family have learned everything they need to know as diabetes education is not a "one off" process. Diabetes education requires constant review, depending on the needs of the person with diabetes and the family with ongoing maturation and adaptation. Many centers will give Education Updates at appropriate times that may include annual assessments with clinical review, starting or changing school, during the adolescent period, at the adoption of new diabetes technologies or with any dietary changes.

5.2 | Structured diabetes education programs

There are three key criteria that should characterize a structured educational program[6]:

- the program has a structured, written curriculum that is aligned with current clinical guidelines
- uses trained diabetes educators
- is quality assured

The evidence-base for the effectiveness of structured education versus informal unstructured education in improving glycemic control[34–36] and preventing severe hypoglycemia and restoring awareness of hypoglycemia[37] comes mainly from studies involving adults with diabetes. These studies have been performed mainly in North America, Australia, and Europe and have been extensively reviewed in various publications.[6,8,34] Diabetes self-management education programs are efficacious and cost-effective in promoting and facilitating self-management, improving children's diabetes knowledge, skills, and motivation, and have been shown to improve biomedical, behavioral, and psychosocial outcomes.[38]

There are few studies involving children and adolescents with type 1 diabetes (T1D) and their parents, and the evidence base for the effectiveness of structured education programs is limited.[6,8,39,40] Indirect evidence suggests that countries in which structured education are available for all have better outcomes with respect glycemic control.[41–43] Evidence to assess the impact of a structured education program in children with T1D, suggest that the structured education and support program in the year after diagnosis can improve short-term glycemic outcomes, measured as HbA1c, but this effect may not persist after discontinuing intensive coaching. This highlights the need for ongoing person-centered education.[44] A short-term (1 year) evaluation of a structured initial education program improved child and parent-reported outcomes.[40] Structured

TABLE 2 Key education topics for review at diabetes diagnosis and ongoing engagement

At diagnosis	Continuing curriculum
Simple explanation of how the diagnosis was made, the cause of symptoms and need for lifelong insulin replacement. Reassure that with insulin replacement the child will quickly regain health and energy.	Pathophysiology, epidemiology, classification, and metabolism
Explore feelings of guilt or blame and discuss uncertainty about the cause of diabetes.	Explore child's/adolescent's understanding as they mature
Normalize grief and loss reaction to the diagnosis	Address psychological health and diabetes burnout
Discuss risk for siblings and interventions available to minimize risk	Revise as needed
Simple explanation of glucose and the relationship between food, blood glucose value, and insulin.	Explain other sources of glucose; that is, liver as a source of glucose
Simple explanation that insulin lowers the blood glucose value, rapid-acting insulin lowers it quickly and long-acting insulin lowers it slowly.	Insulin action and profile Adjustment of insulin Pump extended bolus functions Introduction to diabetes technology (if available)
Discuss the role and responsibility of family in the delivery and supervision of self-management tasks and the expectation for frequent follow-up.	Review who is doing what at each visit and encourage active parental involvement. Explore barriers to clinic attendance if missed appointments
Establish clear and consistent treatment targets and goals.	Revise frequently Goal setting focus on goals that are SMART: specific, measurable, achievable, realistic, and time-based Micro- and macro-vascular complications, screening protocol, and prevention
Focus on basic survival skills needed to manage diabetes from day one. Accomplishment of these skills will increase the caregiver's and child's confidence in their ability to manage. Assess competence in • SMBG and/or CGM, ketone monitoring • insulin devices: injection, pen, or pump • diabetes diary or downloading of data from pens, pump, glucose meters, and CGM • carbohydrate counting tools • insulin storage	Review these skills • As new devices or technologies are introduced • As child/adolescent takes on self-management tasks • If diabetes needs stabilization • In response to episodes of DKA or severe hypoglycemia • On diabetes camps • When new caregivers are introduced to the family • When child/adolescent is planning school camp/excursion • During transition to adult service • Whenever there are admissions other than due to diabetes or DKA
Basic dietetic advice including carbohydrate counting, importance of healthy eating, and meal-time routines. Promotion of healthy body weight. Clarification of myths about food and diabetes, as well as beliefs about cure in the honeymoon phase.	Explain effect on glucose levels of different food components including protein, fat, fiber, and glycemic index; and discuss insulin therapy management strategies to optimize postprandial glucose levels Revise nutritional skills as the child grows and develops Adapt nutritional interventions in response to new diagnosis, for example, celiac disease Screen for disordered eating
Explanation of hypoglycemia (symptoms, prevention, management), identify cards, bracelet, necklace. Explanation of hyperglycemia and diabetes ketoacidosis (symptoms, prevention, management).	Revise with introduction of new activities and new caregivers Practice reconstitution of glucagon Risk factors: hypoglycemia unawareness, young age Precautions with alcohol, and driving
Diabetes during illnesses; advise not to omit insulin and to call the diabetes team for advice.	Effect of intercurrent illness, hyperglycemia, ketosis, and prevention and identification of DKA Diet and fluids of sick days Sick day management plan (see chapter: Sick day management)
Integration of diabetes self-management tasks into family life, social activities, sports, and school.	Problem-solving and adjustments to treatment in everyday life, motivation, and coping with unexpected glucose fluctuations Review and revise school management plan annually Exercise, camp, holiday planning, and travel
Address questions about impact on future risk behaviors and aspirations for the child/adolescent	Information to teenagers about alcohol, tobacco, cannabis, and other illegal recreational substances (see chapter about adolescents) Information about contraception, sexuality, and pregnancy planning Information about employment
Membership in a diabetes association and other available support services	Explore opportunities for peer support and family support
Details of emergency telephone contacts and follow-up arrangements.	Update as required

education should be available to all persons with diabetes at the time of diagnosis and reinforced with regular teaching sessions after diagnosis and then annually or more frequently as determined by formal, regular individual assessment of need.[4–12] A review of relevant qualitative studies in pediatric and adolescent services showed that providing skills training using structured education to people does not necessarily result in participants adopting and sustaining recommended changes in behavior. To sustain diabetes self-management skills after attending structured education, it is recommended that support be provided over the longer-term by appropriately trained health care professionals in response to individuals' needs.[6,27,45] A study of structured education during the pediatric to adult transition period highlighted the importance of carbohydrate counting in predicting glycemic control.[46] This study emphasized that many persons diagnosed and educated in childhood may be more knowledgeable in diabetes management, but their practical skill in matching insulin dose and carbohydrate content is often suboptimal.[46]

Effective educational programs are carefully planned, have specific aims and age-appropriate learning objectives, which are shared with people with diabetes, their families, and other care givers[4,6,8,17,47] and are integrated into routine care. Ways to improve access to and uptake of diabetes self-management programs are needed globally in resource deficient regions.[38] Many less-resourced countries, which have a high rates of morbidity and mortality, may only be able to provide minimal education and ongoing support. All young people with T1D and their caregivers deserve quality care, with structured diabetes education from a diabetes team or health care professional experienced in pediatric diabetes.[48]

5.3 | Support programs and diabetes education

The interpretation of educational research is complex relating to the intersection of interventions frequently combining education, psychosocial, and psychotherapeutic methods.[34,35] The outcomes most likely to be directly affected by diabetes education are knowledge and understanding, self-management behaviors, and psychosocial adaptation.[4,14] These psychosocial and behavioral outcomes are key requirements for glycemic control.[14] Systematic reviews of psychoeducational interventions conclude that such measures have shown small to medium beneficial effects on glycemic control[49–55] and a somewhat greater effect on psychological outcomes.[35,56,57] The effects are more pronounced for children than for adults.[56]

Recently, a variety of support methods have been tried in conjunction with defined education programs that include motivational interviewing, life coaching, and a guided self-determination model. While all of these approaches appear to improve the psychological well-being and coping strategies of young people, there is often minimal improvement in glycemic control, measured as HbA1c. In addition, the impact is often of short duration, requiring repeated interventions.[58–62] Because both high glycemic variability and low glycemic variability may be associated with the same HbA1c value it is important to evaluate frequency of hypoglycemia and time in range, if available, when evaluating glycemic control.[63] Education may be seen as an interface between clinical practice and research. Continuing research into diabetes and educational methods is important in improving clinical practice and should be prioritized by diabetes centers, individually as well as part of regional, national, and international networks and registries.[4–7,12,14]

5.4 | Delivery of diabetes education

Diabetes education is delivered by all members of the diabetes multidisciplinary team who complement each other by working within their scope of practice as guided by their subspecialty. All team members are responsible for assessing the educational needs of the family at each episode of contact and arranging referral to the most appropriate diabetes health care professional to address the family's identified learning needs.[4,6–8,11,12,25] The team should have a sound understanding of the principles governing teaching and learning.

The diabetes team should demonstrate skills consistent with the principles of teaching and structured education and also incorporate behavioral change management including counseling techniques into their therapeutic practice.[26,27] Tertiary level diabetes education and clinical management courses are available in some countries along with accreditation programs available to health care professionals wishing to achieve certification. Certified diabetes educators require proficiency in clinical practice, research, diabetes education, and counseling and frequently manage the coordination, delivery, and evaluation of education programs within their health facilities.[64] Guidelines should be developed and evaluated for core competencies for diabetes educators to help ensure quality education is provided to young people with diabetes and their caregivers.[26]

Multidisciplinary teams providing education should include, at a minimum, a pediatric endocrinologist/diabetologist or a physician trained in the care of children and adolescents with diabetes, a diabetes specialist nurse/diabetes educator/pediatric nurse, a dietitian, a psychologist, and a social worker.[6] Other professionals such as a play therapist or a Child Life Specialist can play an important role in the diabetes team by providing pedagogical preparation of children and young people for procedures and examinations and support in the educational process for the child with diabetes, parents, and siblings.[65] Furthermore, an occupational therapist can provide pedagogical and practical support, especially to children and adolescents with neuropsychiatric diagnoses.[66] In addition, there is value in trained health or life coaches in helping people with diabetes meet self-management goals.[59]

5.5 | Diabetes education—at diagnosis, settings, timing, and cultural considerations

5.5.1 | Diabetes education at diagnosis

At diagnosis families may be unreceptive to education due to the emotional stress of the diagnosis or for practical reasons such as fatigue from sleep deprivation due to hospitalization. For this reason,

the education program should be tailored to meet the pace dictated by the family's readiness to learn. The initial focus should be on the acquisition of the practical "survival skills" required to manage the diabetes at home and address the immediate concerns expressed by the family. Time should be given for the skills to be practiced and basic concepts should be reviewed within the first weeks of diagnosis. The family should be given a structured plan for education so that they can arrange dedicated time for the education. At diagnosis, concepts are new, and the child or adolescent will need consistent messages and support from parents and other primary care givers. To ensure this occurs both parents or other primary care givers should be encouraged to attend all education sessions.

Initial learning should be reinforced by written guidelines and curricula. It should be accompanied by quality assured education materials (books, booklets, leaflets, websites, social medias, smart phone/tablet applications, games, and other resources) appropriate to the child's and adolescent's age and maturity.[6,8] Educational (electronic or printed format) materials should use appropriate language and a style that is easily comprehensible. For parents with limited literacy and/or poor numeracy special materials using diagrams, drawings, video clips, and other visual media are recommended.[67,68] All material should follow common therapeutic goals and a shared holistic approach.

Table 2 lists suggestions for the basic initial content of diabetes education at diagnosis and the extension of this content to be delivered and revised at regular intervals over the course of the family's contact with diabetes services. These topics provide a comprehensive basis for successful therapy and positive emotional coping for youth with diabetes and their caregivers. The topics should be adapted to ensure the diabetes education is appropriate to each individual's age, maturity, learning needs, and local circumstances. ISPAD 2022 Consensus Guidelines Chapter 10 on "Nutritional management in children and adolescents with diabetes" has a detailed explanation of the content and methods of delivering nutritional education.

The number of appropriate education hours for a newly diagnosed child or adolescent may depend on the health care system and individual characteristics of the person with diabetes and family. Data from a study in Germany showed that an average of approximately 30 h of theoretical and practical instruction was provided for the parents and/or the child/adolescent with T1D.[69] A study from Canada revealed that certified diabetes educators spent a median of 10.5 h per person with diabetes during the first year after diabetes onset.[70] Interestingly, this study also showed that greater teaching time was needed for young people with diabetes from higher socioeconomic backgrounds as compared with a lower socioeconomic level. It is, however, important that the number of education hours is adapted to the individual needs of the person with diabetes and their family.

5.5.2 | Settings, timing, and cultural background

Initial education and diagnosis

Due to the heterogeneity of health care systems and funding of diabetes care and education there is evidence supporting both inpatient and ambulatory approaches to diabetes stabilization and initial education at diagnosis, and studies have shown no difference across relevant outcomes.[32,62,69,71–76] A recently published study in the UK health system shows strong evidence that there is no difference between home-based and hospital-based initiation of care in children newly diagnosed with T1D across relevant outcomes.[62]

Continuing education

Ongoing educational encounters most often take place in an ambulatory (outpatient, domiciliary, community) setting.[4–8,11,12,77,78] Where staffing levels, expertise and local circumstances do not permit this to occur, educational programs may be carried out in the hospital environment, either by individual teaching or in groups and whenever possible in a protected environment conducive to learning.[71,73,76,78] It is important to adapt the programs to families who may have low literacy and numeracy.[79] For families from different cultural backgrounds, the education needs to be adapted to their food habits and their health belief models.[29]

Age-appropriate, group education approaches directed at the specific needs of individuals can be at least equally effective as individual education and may be more cost effective.[6] In qualitative studies young persons with diabetes often report they appreciate group education. Adolescents also express that meeting others with the same condition and shared experiences can help mitigate the isolation of diabetes.[61,80,81] During the transition period from adolescence into adulthood there are specific education needs such as self-management and decision support, and group clinics.[82–85] Young people also benefit from workshops to prepare for the transition.[86] During the transition, parents also may need support in changing their role.[22,87,88]

The educational experience may be enhanced by peer group education or school friendships.[31,89] Diabetes residential and day camps organized by local and national diabetes organizations provide an additional opportunity for learning and review of diabetes management skills in a safe and supportive environment. From a diabetes education standpoint, diabetes camps appear to have an initial impact and are appreciated by young people with diabetes and their caregivers, which is mediated through psychosocial benefits.[90–92] The organization and aims of diabetes camps have been described in detail in the ISPAD Guideline for the delivery of ambulatory care (ISPAD 2022 Consensus Guidelines Chapter 7 on The delivery of ambulatory diabetes care to children and adolescents with diabetes). Educational activities at camp are most effective if they are matched to gender and age and embody empowerment principles.[93] Benefits include the opportunity for youth to foster relationships and share experiences in a safe environment.[94]

Digital education, which includes use of technology to promote self-management and support education, has become increasingly available in diabetes care and offers the ability to promote empowerment and self-management to youth and their caregivers.[84,95]

Type 2 diabetes

Youth with T2D may experience distinct challenges as compared with adolescents with T1D or adults with T2D. Treatment modalities that

include oral medications differ from T1D treatment and there is often a need for major lifestyle changes, related to food and physical activities. Youth with T2D and their caregivers often reside in minority communities with lower socioeconomic status and experience challenges related to financial and or residential instability. Diabetes educators should be aware of these potential complex psychosocial and cultural environments, which can make the lifestyle changes difficult to implement and may result in decreased engagement by youth with T2D self-managing their disease.[96–98] These adolescents may have a higher rate of psychological disorders, depression, stigmatization and eating disorders, and need psychological support and/or psychotherapy together with their parents.[99] The role of health care professionals and caregivers is to promote attendance at education sessions and encourage independent self-management regimens and self-care practices for optimal clinical outcomes.[96,97,100] Implementation of culturally specific education have shown improvements in self-management behaviors, which can help to minimize long-term risk of complications.[101] Studies also show that there is a lack of structured evidence-based diabetes education for people with learning disabilities, literacy problems and for non-English speakers.[97] See ISPAD 2022 Consensus Guidelines Chapter 3 on T2D in youth.

5.6 | Diabetes education and intensive treatment methods

Matching and adjusting insulin profiles to quantified food intake and exercise levels is an important part of any intensified diabetes management plan. More complex therapeutic regimens with multiple daily injections, use of different insulins and insulin analogs, CSII, as well as using CGM devices require comprehensive education and practical training. Structured age-specific education programs for adults, adolescents, or parents of younger children with T1D on the use of real-time CGM systems and data interpretation have shown improvements in knowledge, satisfaction, glycemic control, and acceptance of real-time CGM systems.[102–104] Using automated insulin delivery systems or hybrid-closed loop systems requires comprehensive education and reeducation of all family members on nutrition and carbohydrate counting, safety behaviors, and an understanding of the integration of these elements into the daily activities of the child/adolescent using the system.[105–107] A key prerequisite for these diabetes technologies is that all team members are appropriately trained and able competently to manage these systems.

Higher levels of education, health literacy, and understanding are often required for these interventions to be successful, which require significant investments of time, skill, and resources from the education team.[4,8,11,108] In this context, simply changing from one form of insulin regimen to another as the only means of intervention may not be appropriate and may not improve glycemic control.[25,49] The appropriate educational approach to the implementation of diabetes technology is holistic and should address treatment and lifestyle goals that addresses barriers, optimizes glycemic management and is centered around the child with diabetes. In this way, an intensified management plan utilizing comprehensive structured education has a greater likelihood of success, especially if the educators are highly skilled and motivated.[109,110]

5.7 | Diabetes education and digital technologies

Advancements in technology combined with widespread adoption of digital devices by youths with diabetes, their caregivers and their clinicians have created an opportunity to leverage digital platforms to augment diabetes care. The available newer technologies include smart phone/web-based applications,[55,111–114] computer games,[115] text messaging,[116] and telephone reminders and telemedical support.[117] These technologies are most effective when they include interactive modes and utilize social media.[34,53,118] Evidence from group discussions with young people suggests that education using these newer technologies is attractive, and there is further scientific data to support its widespread use.[114,118–121] However, there is still a lack of robust data on effectiveness in relation to key outcome parameters.[122,123]

Technology-based diabetes teaching systems are interactive and aim to engage the user by age specific, animated, and entertaining applications. They are designed to serve different purposes such as tracking and monitoring blood glucose, activity/exercise, healthy eating, medication adherence, monitoring for complications, annual screenings, and problem-solving. Calorie/carbohydrate counting smart phone applications help people tackle the abstract concept of carbohydrate content in food. Smart phone applications have provided a comprehensive food database and easier access to nutrient data on less common foods including those found in restaurant chains. It can be important to check the source of the current application. Data from national nutrient databases can provide a more accurate carbohydrate content than data from open/crowd sourced information.[124]

Digital diabetes tools have been designed for coaching people with diabetes by personalized diabetes education.[125] Users define long-term goals, such as optimizing nutrition, decreasing blood glucose levels, and receive daily messages to attain specific goals and to reiterate essential concepts of diabetes education. The feedback loop sustained by two-way communication, where both sender and receiver are engaged, facilitated by way of technology offers the greatest favorable impact on glycemic control.[126] Small studies in pediatric and adult persons with diabetes have shown the benefit of using technology-based diabetes education on improving confidence, self-management, quality of life, and glycemic control outcomes.[55,111–113,127,128]

Telemedicine, that encompasses the use of video or phone appointments between a person with diabetes and their health care professional, has been particularly helpful for people with diabetes who live in remote areas and do not have access to professional counseling and diabetes education resources or were unable to visit clinics due to the COVID pandemic.[129,130] The communication and exchange of medical information are made possible through

TABLE 3 Concerns, challenges, and learning opportunities for infants and toddlers, school age children and adolescents with diabetes

Group of children	Concern/challenges	Learning opportunities
Infant a toddlers 0–3 years	Total dependence on parents and caregivers for injections/management of pumps, food, and monitoring. Parents may feel increased stress, diminished bonding, and depressive feelings. Unpredictable erratic eating and activity levels. Difficulties in distinguishing normal infant behavior from diabetes-related mood swings, for example, due to hypoglycemia. Injections, infusion set and sensor insertions, and BG checks seen as pain inflicted by caregivers. Hypoglycemia is difficult for the child to communicate. Long-standing hyperglycemia may be even more harmful Care in nursery and kindergarten	Requirement of a trusting attachment between infant and caregivers. Support and education for parents Education about technical devices Education on prevention, recognition, risk, and management of hypoglycemia and hyperglycemia. Education for nursery and kindergarten staff Engagement with dietitian, Psychologists, child life support as needed
Preschool age 3–6 years	Care in nursery and kindergarten Need help to identify symptoms of high/low glucose values Learning the meaning of high/low glucose values	Education for nursery and kindergarten staff Family support Education for parents, from the whole team Age-appropriate education for the child Engagement with dietitian, psychologist, child life support as needed
School age 7–12 years	Adjusting to the change from home or kindergarten to school. Developing self-esteem and peer relationships. Increasing understanding and learning to help with injections, pump use, and monitoring Gradual development of the child's independence with progressive stepwise transfer of appropriate responsibilities Adapting diabetes to school programs, school meals, exercise, and sports. Not wanting to do self-management task in public. Negotiating supervision of diabetes management tasks. Progressive recognition and awareness of hypoglycemia symptoms	Education for school personal and others. Family support Advising parents on the gradual development of the child's independence. Age-appropriate education for the child Clarify the responsibility for self-management. Peer-education Engagement with dietitian, psychologist, and mental health support as needed
Adolescents	Accepting the critical role of continued parental involvement. High risk behavior, tobacco, alcohol, legal, and illegal drugs Importance of appropriate contraception Promoting independent, responsible self-management appropriate to level of maturity and understanding. Emotional and peer group conflicts Body image issues and weight gain and risk for disordered eating, insulin omission Ability to prioritize one's health	Learning from each other/ accepting each other's responsibility Psychologists on the team Reproductive health education Supportive technology tools Assessment of potential risky behaviors using "HEADSSS" communication tool to ask about: home, education and eating, activities/employment, drugs tobacco, alcohol, suicidality, sex, and safety Engagement with dietitian, psychologist and mental health support as needed Dietitian on the team Readiness and preparation for transition to adult clinic

videoconferencing during a telemedicine session. Clinicians provide real-time problem-oriented education for young people with diabetes by using telemedicine to facilitate better decisions by youths with diabetes and health care providers. Telemedicine has been successfully integrated into diabetes management by many diabetes centers of excellence to extend the reach of diabetes education and support when access to care is limited.[131] Telemedicine care has proven to be an effective add-on to regular out-patient care, but not a complete replacement for in person face-to-face counseling.[132–135]

There are some possible limitations to using high-tech diabetes tools for education purposes that are being addressed with the collaboration of technology experts, scientists, clinicians, and people with diabetes. Clinicians should warn their youth with diabetes regarding the potential inaccuracies, potential breach of confidentiality, and the risk of being overwhelmed by web-based information and guide their young people with diabetes and their caregivers to websites and mobile applications that are trustworthy.[122,124]

6 | AGE-SPECIFIC CHALLENGES AND OPPORTUNITIES

The features of normal development common to various ages and stages present unique challenges to diabetes management. For this reason, specific curricula and appropriate education materials and tools are recommended for children and adolescents of different age groups as well as for their parents and other primary care givers. School age children have expressed dissatisfaction that health professionals talk to parents and not to them, and there is some evidence that focused age-appropriate educational interventions are effective in children and families.[50,52–54,57,136] Table 3 identifies concerns, challenges, and learning opportunities common to the major developmental stages. The ISPAD guidelines chapters on caring for toddlers and preschool children and the chapter on adolescents with diabetes, provide more detailed information. (See ISPAD 2022 Consensus Guidelines Chapter 21 on Diabetes in Adolescence and Chapter 23 on Management of diabetes in very young children with diabetes).

7 | CONCLUSIONS

In conclusion, effective management of diabetes requires time, commitment, effort, and motivation. Age-appropriate, quality-assured structured diabetes education must be available to all young people with diabetes and their caregivers to maximize the effectiveness of their treatment. Diabetes education should be delivered by a multidisciplinary team of health care professionals who complement each other by working within their scope of practice as guided by their subspecialty. Diabetes education, designed to empower young people and caregivers in promoting self-management, starts at diagnosis and needs to be a continuous process, repeated regularly to ensure a positive long-term outlook. When new diabetes technologies become available, comprehensive structured education for educators, parents and children is a prerequisite for success.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13418.

AUTHOR CONTRIBUTIONS

For this guideline all authors have contributed with planning, literature review, drafting and writing the mauscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Lindholm Olinder A, DeAbreu M, Greene S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes education in children and adolescents. *Pediatr Diabetes*. 2022;23(8):1229-1242. doi:10.1111/pedi.13418

Received: 9 September 2022 | Accepted: 12 September 2022

DOI: 10.1111/pedi.13417

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: The delivery of ambulatory diabetes care to children and adolescents with diabetes

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1 | WHAT IS NEW OR DIFFERENT

- In this update, the general guidelines regarding the gold standard of ambulatory care for children, adolescents, and young adults with type 1 diabetes (T1D) have been revised.
- Guidance on current diabetes technology has been expanded to include relevant information on telemedicine, data support, education and literacy.
- Updated guidance on type 2 diabetes (T2D) ambulatory care is provided.

2 | EXECUTIVE SUMMARY

2.1 | Introduction

- From diagnosis, the child or adolescent with diabetes and their caregivers must receive education and care from a multidisciplinary diabetes team comprised of specialists with training and expertise in both diabetes and pediatrics, including child and adolescent development. B
- The diabetes team should implement a person-centered care model, where the persons with diabetes and their family are the central members of the care team. B
- Clear and consistent communication around education and treatment plans is essential. C
- Current technologies commensurate with available resources and the individual child's/family's needs should be integrated into the treatment plan. C
- It is important to empower children and families with the awareness that diabetes is a condition that can be managed and avoid the young person with diabetes being defined by the condition ("the diabetic child" or "the sick child"); and use language that engages and motivates children and families towards dynamic diabetes management. C

- If a multidisciplinary team is not locally available, the clinicians providing diabetes care should have ready access to advice and expertise from the multidisciplinary diabetes care team in regional centers of excellence, and this could be facilitated using telemedicine. C

2.2 | Objectives of ambulatory care

- The ultimate goal is to provide care that results in "on target" glucose profiles, good quality of life, normal growth and development, and lowest possible risk of acute and long-term diabetes complications. E

2.3 | Key points in diabetes care delivery

- Specialized hospital medical care. E
- Expert comprehensive ambulatory care for diabetes and associated conditions. E
- Support available 24 h a day for young people with diabetes and their caregivers. C
- Comprehensive education for the young person and his/her caregivers on day-to-day management of diabetes including insulin therapy, glucose monitoring, nutrition. C
- Ongoing diabetes education and self-management training on issues such as hypoglycemia, exercise, sick-day management, travel, fasting, festivals and other special occasions. E
- Integration of diabetes technology in pediatric diabetes care and appropriate education of young people with diabetes and their families about diabetes technology. C
- Consistent articulation of glycemic targets. C
- Introduction of new therapies and technologies as diabetes management evolves. E
- Screening for comorbidities and complications and related risk factors. B
- Psychosocial support for all young people with diabetes and families. B
- Advice for care at school, camps, and other venues where children with diabetes require care when away from home. E
- Guidance on other age and developmentally appropriate goals and life events (including contraception, driving safety, use of alcohol, tobacco and other substances, and other risk-taking behaviors). E
- Additional psychosocial evaluation and support for children who are at high-risk of acute and/or chronic complications due to suboptimal glycemic management, frequent utilization of emergency departments/hospital, other social considerations and/or mental health needs. B
- Recommendation on routine vaccinations to be provided for children with diabetes according to age-related and regional recommendations. Advice on annual vaccination against influenza for all individuals with diabetes above 6 months of age. Pneumococcal and meningococcal vaccines are also recommended. C
- Enable telemedicine consultation for diabetes clinic visits and psychosocial counseling. C
- Advice and support for physicians and health care professionals who provide diabetes care where immediate access to a specialized diabetes care team is not possible. B
- Provision and updating the team (including the child with diabetes and the family) with current information on research in diabetes. E

2.4 | Key points in processes of diabetes care

Following diabetes diagnosis and stabilization, the child or young person with diabetes and caregivers should be provided with: C

- Essential skills such as glucose and ketone monitoring
- Administration of insulin including the concepts of dosing for meals, management of hypoglycemia and hyperglycemia
- Access to an on-call team (24 h a day)
- Routine visits, at least every 3 months, should include:
  - Ongoing evaluation of diabetes management that includes review of insulin doses and glucose profiles, data interpretation and decision-making empowerment based on standardized glucose reports.
  - Evaluation of growth and physical development, and general health (including concomitant medical conditions and medications)
  - Physical examination with inspection of glucose monitoring sites and injection sites
  - Nutrition consultation
  - Options to communicate between visits, for example, for insulin dose adjustments, should be provided, including text messages or virtual visits via video, telephone, or live chat.
- An annual review visit that in addition to the above routine care includes:
  - Expanded physical assessments (such as pubertal staging, foot examination)
  - Additional self-management assessments, such as dietary knowledge (ability to estimate carbohydrate consumption and accurately determine insulin doses), glucose data interpretation, autonomy in diabetes management, knowledge about sick day rules
  - Psychosocial assessment
  - Screening for comorbidities, long-terms complications, and related risk factors

2.5 | Other key aspects of ambulatory care

- Identification of barriers to care. B
- Considering specific needs of minority groups. C
- A planned, structured transition approach to adult diabetes care to facilitate continuity of care during this critical time. B The age of

transition to an adult clinic varies according to individual maturity and local circumstances
- Contact with other families of children with diabetes. E
- Promotion of diabetes camps. E
- Interactions with schools as part of day-to-day diabetes care. B
- Facilitating access to care by in-person and virtual diabetes visits through telemedicine or telehealth. B

2.6 | Quality of care

- Diabetes centers need methods to evaluate and enhance the quality and equity of the diabetes services they provide and the outcomes of their management. C
- Given the complexity of T1D management, this entails a multifaceted approach that integrates psychosocial supports, recognizes social determinants of health, leverages information science, and the application of quality improvement (QI) methodology. E
- Diabetes registries can be an important tool for population management at individual centers, QI, and benchmarking across collaborating centers. B
- Benchmark reporting that evaluates effectiveness of diabetes care measured against guidelines for standard practices can promote accountability and system wide improvements in diabetes care. C
- Involvement of governments, policy makers and health insurance providers facilitate provision of adequate resources that are required for high quality diabetes care. E

2.7 | Type 2 diabetes

- The main goals of T2D management include education for diabetes self-management, normalization of glycaemia, weight loss, promotion of physical activity and management of comorbidities and complications. B
- The aims of therapy in youth-onset T2D are to improve glycaemia, prevent acute and chronic complications, prevent metabolic decompensation, improve insulin sensitivity and provide exogenous insulin when necessary. C
- Like T1D, the process of ambulatory care for children and youth with T2D includes an outpatient follow-up every 3 months and an annual review of care. C
- Initial treatment of youth with T2D should focus on lifestyle modifications to decrease weight and may include metformin and/or insulin alone or in combination. B
- Blood glucose monitoring (BGM) should be individualized, with a frequency based on specific treatment, degree of glycemic management and available resources. HbA1c concentration should be determined every 3 months. C

2.8 | Glucose monitoring technologies in the ambulatory care

- Continuous glucose monitoring (CGM) data can greatly enhance the effectiveness of the ambulatory care visit, facilitates remote communication between the family and the diabetes care team, allowing for an effective teleconsultation, and promotes "shared decision-making". C
- Clinicians should review the ambulatory glucose profile (AGP), available for most CGM systems. C
- Clinicians should focus on patterns and trends of glucose levels and less about single days. It is recommended that clinicians review 14 days of data for adequate decision-making. C

3 | INTRODUCTION

This chapter of the ISPAD Consensus 2022 Guidelines outlines recommendations for ambulatory diabetes care, including routine clinical assessments according to best current practice. Specific recommendations for certain elements of ambulatory care, including insulin therapy, monitoring of glycemic management, nutritional management, diabetes education, screening for and management of comorbidities and vascular complications, T2D, specific age groups, diabetes in school, and use of diabetes technology are addressed in detail elsewhere in the ISPAD guidelines, which should be consulted in conjunction with this chapter.

Diabetes is primarily managed in the outpatient or ambulatory setting, where all children with diabetes should receive specialized person-centered care from a multidisciplinary team, qualified to provide up-to-date pediatric specific education and support. The period following diabetes diagnosis and stabilization is a critical opportunity to commence education and preparation for outpatient care. Thereafter, regular, ongoing ambulatory diabetes care assessment should be provided throughout childhood and adolescence and be complemented with a well-supported program to facilitate transition to adult care at the appropriate time.

The overall goal of well-structured and high-quality ambulatory diabetes care for young people with diabetes is to promote high quality of life, normal growth and development, and prevent the risk of acute and chronic complications.

An investment in excellent diabetes care, particularly during childhood and adolescence, should be advocated globally and is likely to have a significant economic benefit.

The components of clinical care include structure, processes, content and outcomes and they are extensively discussed in this chapter. Structure of care describes how delivery systems are organized and financed; processes of care describe how care is delivered; content of care describes what is being delivered, including education and treatment that affect outcomes.[1] Intermittent critical re-examination of these components provides an opportunity to continually improve the

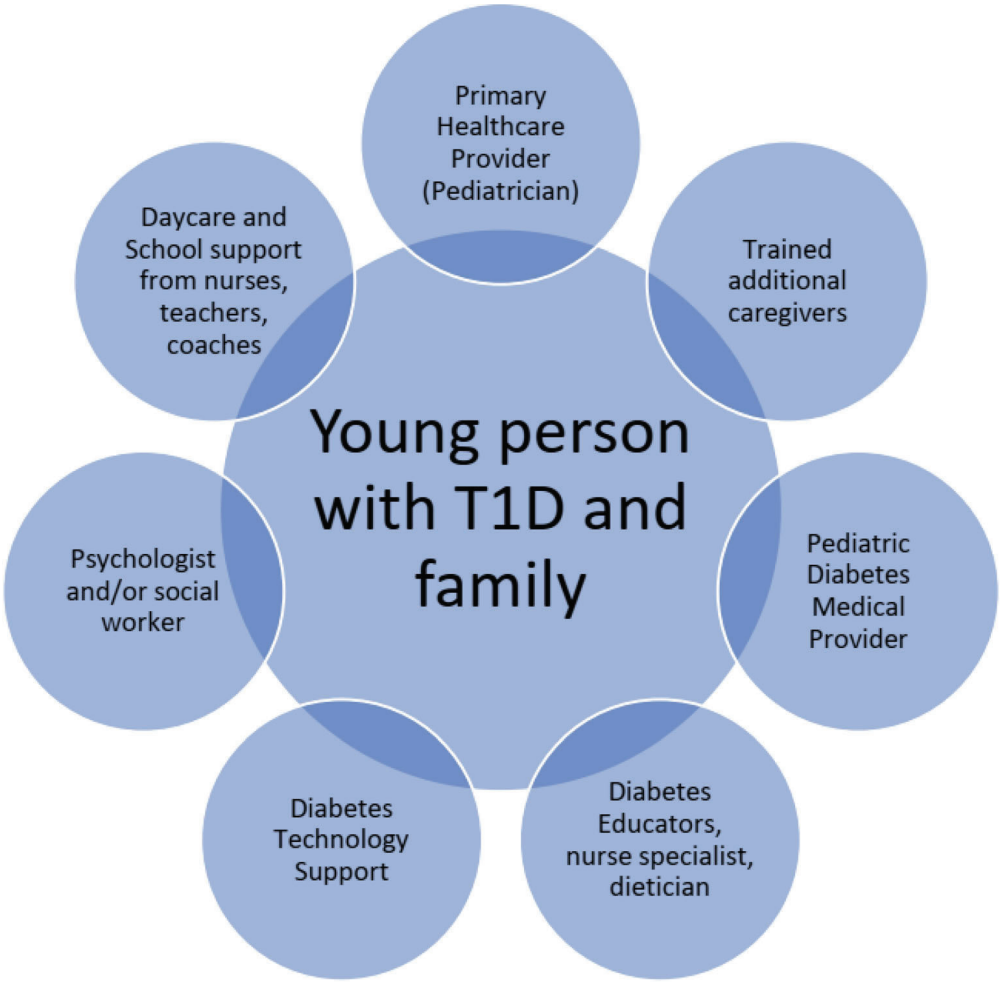

FIGURE 1 Structure of care: Person-centered pediatric diabetes care model. Diabetes care is best delivered by a multidisciplinary team with the youth with T1D and family at the center. The team should consist of a pediatrician specialized in diabetes or endocrinology (preferred), or physician/advanced nurse practitioner with a special interest (and training) in childhood and adolescent diabetes, diabetes nurse specialist or diabetes nurse educator, dietitian trained in pediatrics with knowledge of childhood diabetes and normal growth, psychologist trained in pediatrics and with knowledge of childhood diabetes and chronic illness, pediatric social worker with training in childhood diabetes and chronic illness. The team should regularly receive training and education on technology and have the resources to develop strong links, effective communication, and shared practices with primary healthcare providers, schools, and other essential caregivers.

quality of care delivered using available tools and resources. Because diabetes is a chronic condition, approaches to all aspects of clinical care will undoubtedly change over time.

This chapter aims to establish ideal guidelines for a comprehensive diabetes service. A dedicated *ISPAD 2022 Consensus Guidelines Chapter 25 on Management of Diabetes in Limited Resource Settings* is available separately to complement this guidance.

4 | STRUCTURE OF CARE

The structure of diabetes care delivery should support accomplishment of the following:

- Overall goals: To promote high quality of life, normal growth and development, a balanced approach to the psychological handling of a demanding chronic condition, early detection of co-morbidities and avoidance of severe short- and long-term complications.
- Individualized treatment plan: A glucose monitoring and insulin regimen that should, ideally, mimic physiologic insulin secretion to maintain healthy metabolism, and is in accordance with the treatment preferences of the child and family, which may change over time.
- Access to multidisciplinary diabetes expertise: Medical care providers, educators, mental and behavioral health resources that are available both during episodic visits and between encounters.

4.1 | Person-centered diabetes care

Diabetes care is complex and is best delivered by a multidisciplinary team of specialists with training and expertise in both diabetes and pediatrics, and knowledgeable about child and adolescent development. Diabetes self-management requires mastery of an extensive set of skills. Therefore, from diagnosis, it should be emphasized that the child and immediate family are the central members of the care team.[2] (Figure 1) The diabetes care team should have the resources to develop strong links, effective communication, and shared practices with extended family members or other care providers who play an important role in the child's diabetes care and may serve as a liaison between the child and the medical team, including school nurses, daycare staff, teachers, sports coaches, camp personnel, and others who care for children. Teams should be sensitive to language and numeracy barriers and information delivered with language appropriate

resources and pitched at relevant levels of understanding.[3] It is important to review such knowledge and understanding on a regular basis at clinic visits.

Engaging directly with the young person with diabetes and their caregivers to gauge understanding and diabetes knowledge, health behaviors, goals, perceived benefits, and risks should be built into standard structures of care delivery. It is imperative to promote the understanding that the child retains his/her full prior potential to achieve goals physically and intellectually. Over time, continued engagement by the diabetes team with children as they mature, using developmentally appropriate educational tools, while recognizing that the child must be treated in the context of their existing psychosocial environment is essential. Effective and clear communication at all levels, between team and families and within the family structure are crucial predictors of early glycemic management and future psychosocial functioning.[4,5]

It is important to empower children and families that diabetes is a condition that can be managed, rather than being defined by the condition ("the diabetic child" or "the sick child"), and to use language that engages and motivates children and families.[3] This requires the multidisciplinary team to have a high level of cultural competence, avoiding shaming and blaming and stigma[6] (#Language Matters campaign). Substitution of judgmental words (such as "uncontrolled", "non-compliant", "non-adherent") with neutral ones (like "time in range (TIR)", "higher HbA1c", "difficulties in", "troubles in") can lower anxiety, build confidence, and promote positive therapeutic relationships.[7,8] Since people encounter various difficulties while managing their diabetes, the team should use language that supports a pathway to navigate challenges rather than underline mistakes. Labeling persons with diabetes with their condition ("the diabetic") increases stigma and may lead to unconscious discriminatory behaviors from the clinician. All these efforts are needed to increase treatment satisfaction and engagement, which are recognized factors impacting health outcomes.[9]

4.2 | Individualized diabetes care

The general aims of the diabetes care team should be to provide individualized diabetes care that best meets the needs of the child and family. This requires structured care delivery:

1. Aims of the diabetes care team:
   - Ongoing diabetes education and self-management training.
   - Up-to-date advice on insulin management, glucose and ketone monitoring techniques.
   - Monitoring for comorbidities, complications, and risk factors for complications.
   - Consistent articulation of individualized goals, such as HbA1c or CGM metrics.[10]
   - Contact with other children and families with diabetes and support groups.
   - Psychosocial screening and referrals to social worker or psychology as indicated.[11]
   - Providing families an opportunity to raise questions about information they may have obtained from the internet or other sources.[12]
   - Current information on relevant research in diabetes.
   - Ongoing training for the diabetes care team on technology and communication skills.
   - Ongoing commitment to advancing clinical practice through the optimal application of existing and new technologies and the development and evaluation of new technologies.

4.3 | Diabetes team organization

The organization of the diabetes care team, its size, and composition will depend on local resources, geographical and demographic characteristics; indeed, there is significant variation worldwide.[13] In general, for members of the pediatric diabetes team to obtain sufficient experience, the center should provide care to at least 150 children and youth with diabetes. The number of diabetes care providers depends on local circumstances; a suggested guide to optimal resource allocation per 100 patients is: 1.0–1.25 diabetes nurse, 0.75–1.0 pediatric diabetologist, 0.5 dietitian, 0.3 social worker/psychologist,[14] which is similar to expert consensus recommendations provided by the international diabetes consortium SWEET peer recognition program. These staffing ratios should be sufficient to meet standards of care. It is recognized, however, that all clinics will not be resourced according to these recommendations. Clinics should be outfitted with digital diabetes data platforms capable of interfacing with cloud-based systems for blood glucose meters, continuous glucose monitors, insulin pumps, and insulin pens to enable glucose pattern review for decision-making at and between visits.

A multidisciplinary team is unlikely to be available in areas of low population density and where childhood diabetes rarely occurs. In these circumstances, care usually is provided by a local pediatrician or general (family) practitioner, who should have ready access, via electronic means of communication, to the diabetes care team at a regional center of excellence.[15,16] Alternatively, teams from district or regional centers often organize outreach clinics to accommodate children and families living in remote areas. Adequate resources are needed to sustain such services.[17] In some areas, two-way telecommunication utilizing video–computer technology or platforms for Voice over Internet Protocol (VoIP) and local medical staff to facilitate the telemedicine visit allows for efficient and effective distant care.[18–21]

COVID-19 dramatically impacted care delivery; widespread use of telemedicine became more prevalent and enabled more efficient and effective distance care.[22–24] Regarding telemedicine and data sharing from devices, awareness of current data protection rights and regulations is important. For example, the European Union's General Data Protection Regulation (https://gdpr.eu/article-9-processing-special-categories-of-personal-data-prohibited/) introduced in Spring 2018 may impact remote monitoring of people with diabetes devices

and telehealth; regulations vary between regions. In all cases, appropriate reimbursement must be available to support these essential non-face-to-face services in order to ensure that diabetes care team can afford to sustain provision of remote care to individuals with diabetes using these technologies.[25]

5 | PROCESSES AND CONTENT OF CARE

It is important to maintain a framework which reassures the child and family that the child is able to live a normal and healthy life.[26] The importance of providing a good start with clear, positive messages, support, and advice, cannot be overemphasized. Setting appropriate expectations and empowering people with diabetes and parents with relevant and developmentally appropriate information is paramount. Generally accepted good clinical approaches for the successful management of children and adolescents with diabetes need to be practiced through the lifespan.

5.1 | Process of care following diagnosis

5.1.1 | Education and practical care guidance

- Depending on the severity of the symptoms and center organization, education should be started immediately after stabilization in either an in- or out-patient setting.
- Soon after diagnosis the child with T1D and caregivers should be provided with an age-appropriate and comprehensive diabetes education module that allows the self- management of diabetes in an outpatient setting (Box 1).
- The management of children who are metabolically stable following diagnosis and do not need admission to hospital, requires members of the diabetes care team to be experienced in outpatient initiation of insulin therapy, management, and education.

BOX 1 Modular age-appropriate education should include

- Insulin as a life-saving therapy
- In due course insulin adjustment, carbohydrate counting, and bolus advisors should be introduced
- Blood glucose monitoring and glycemic targets
- Role of technology in diabetes management
- Nutrition and healthy eating
- School and diabetes care
- Management of hypoglycemia and hyperglycemia
- Managing exercise and sports
- Sick day management
- Psychosocial support and adapting to living with diabetes

- It is important to create a partnership between the care providers and the child and family allowing for shared decision-making and a long-term relationship based on trust.

5.1.2 | Setting expectations

It is important to explain to the child and family the natural course of T1D from diagnosis. This includes the expected changes from a "catch up nutrition phase" with escalating insulin requirements and increased appetite, to the development of a "honeymoon phenomenon" when insulin requirements significantly decrease. The latter is important to highlight as it can frequently bring into question the diagnosis and need for insulin therapy. Revision of the diagnosis and differences between T1D and T2D is often helpful at this stage. It also allows for a conversation about the need for ongoing insulin therapy, regular home glucose monitoring, growth and development of the child with diabetes.

5.1.3 | Psychosocial support for the child and family

This includes identifying the members of the family who will provide care (e.g., one or both parents, a grandparent or another relative, or others) and ensure they receive the necessary education.

It is important to identify and address detrimental health beliefs (e.g., that diabetes is not contagious, and the child does not need to be segregated from other children). Written and/or pictorial age-appropriate materials should be provided in a format (e.g., paper pamphlets, booklets, electronic versions) and language the family understands. Such materials are readily available on several excellent websites of associations involved with pediatric diabetes care, including the ISPAD website (www.ispad.org), Life for a Child (https://lifeforachild.org), and Changing Diabetes in Children (https://www.ispad.org/page/changing).

5.2 | Outpatient care after diagnosis

After stabilization and provision of the education module, outpatient care should be well planned and expectations for contact and support clarified. The following approach is suggested (Box 2):

5.3 | Outpatient care follow-up

5.3.1 | The honeymoon phase

In the first months and up to 1 year after diagnosis, many children experience a partial, temporary remission (the "honeymoon" period) during which insulin requirements may decrease dramatically. Frequent contact with the diabetes care team is necessary to help

BOX 2 Outpatient care after diagnosis of T1D

Approach after diagnosis for youth and families:

- Introduce the diabetes team members and provide a clear follow-up plan
- Expectations for when and how to contact the on-call team (24 h a day)

Outpatient follow-up:

- An outpatient clinic review should occur every 3 months
- An annual review is recommended, which, in addition to routine care, should include screening for relevant comorbidities[a]
- Screen for vascular complications in accordance with recommended guidelines[b]

[a] *See ISPAD 2022 Consensus Guidelines Chapter 19 on "Other complications and associated conditions in children and adolescents with type 1 diabetes".*

[b] *See ISPAD 2022 Consensus Guidelines Chapter 18 on Microvascular and macrovascular complications in children and adolescents.*

manage the changing insulin requirements typical of the early phases of diabetes. Contact may occur through frequent clinic visits, telemedicine, telephone, text messaging, home visits or other methods of communication. Depending on local circumstances, contact often occurs through a combination of these methods. Insulin treatment should not be discontinued even if the insulin requirement is very low and continued regular glucose monitoring should be encouraged. It should be emphasized to the family that it is a temporary phase, and not a "cure", and that insulin requirements will gradually increase over time. A prolonged "honeymoon" period lasting more than 1 year during which insulin requirement remains ≤0.5 unit/kg/day should raise consideration of monogenic diabetes and genetic testing should be considered if pancreatic antibodies were negative.[27]

5.3.2 | Mental and psychosocial health

Screening for a cognitive or mental health disorder soon after diagnosis will identify individuals (either child or caregiver) who may require greater support to adhere to treatment and self-care. A total of 5%–10% of all children suffer from a neurocognitive disorder and at least 2% from a psychiatric disorder. The combination of a cognitive or mental health disorder with diabetes or the presence of a psychiatric disorder in a parent/caregiver increases the likelihood of inadequate or incorrect self-care.[28] These individuals need special attention and treatment.

5.4 | The outpatient visit

It is standard practice for the diabetes care of children and adolescents to be reviewed in an outpatient clinic (face-to-face or remotely) every 3 months, and more often if difficulties in managing diabetes are recognized, or the child is very young (*Please refer ISPAD 2022 Consensus Guidelines Chapter 23 Managing diabetes in preschoolers*). Multidisciplinary team consultation should be available at each visit if required (e.g., nutrition or psychology consultation).

Outpatient and/or telehealth visits with members of the diabetes care team should include an interval history and assessment of the following:

5.4.1 | Diabetes management review

- Self-management skills
- Assess hypoglycemia history including determination of hypoglycemia awareness, method of treating hypoglycemia and access to glucagon.
- Engagement and management of glucose data: enabling the young person and their caregiver(s) to use and upload data from the available technologies including BGM and CGM to cloud systems. Promoting and enabling them to understand and synthesize the information to alter and improve their diabetes management behaviors. Required skills for this to occur include:
  i. Understanding of relevant targets including TIR and HbA1c.
  ii. Ability to connect and upload device data to cloud systems at home.
  iii. Analysis of home glucose monitoring data (BGM from glucose meter readings, real time CGM (rtCGM), "intermittently scanned" CGM (isCGM), urine glucose/ketone monitoring, symptoms of nocturia and hypoglycemia).
- When using BGM and a cloud system is not available, check glucose values stored in the glucose meter memory for accuracy of information reported by parents/child.
- Have an open, non-judgmental dialogue when there are concerns about accuracy of data provided if inconsistent with overall glycemic management measured with a reference method of HbA1c. Exclude technical reasons for inconsistencies including glucometer/CGM malfunction (e.g., expired or improperly stored test strips, poor testing technique, wrong code).

5.4.2 | Intensive insulin therapy

Intensive insulin therapy consists of multiple daily injections (MDI) and insulin pump therapy (continuous subcutaneous insulin infusion – CSII). Young people with diabetes and their families need to be familiar with and able to manage their prescribed insulin therapy. Insulin types, doses, and injection/insulin delivery devices, adequacy of storage and transport of insulin, injection technique should be reviewed regularly. Insulin adjustments for glucose values, food, and exercise

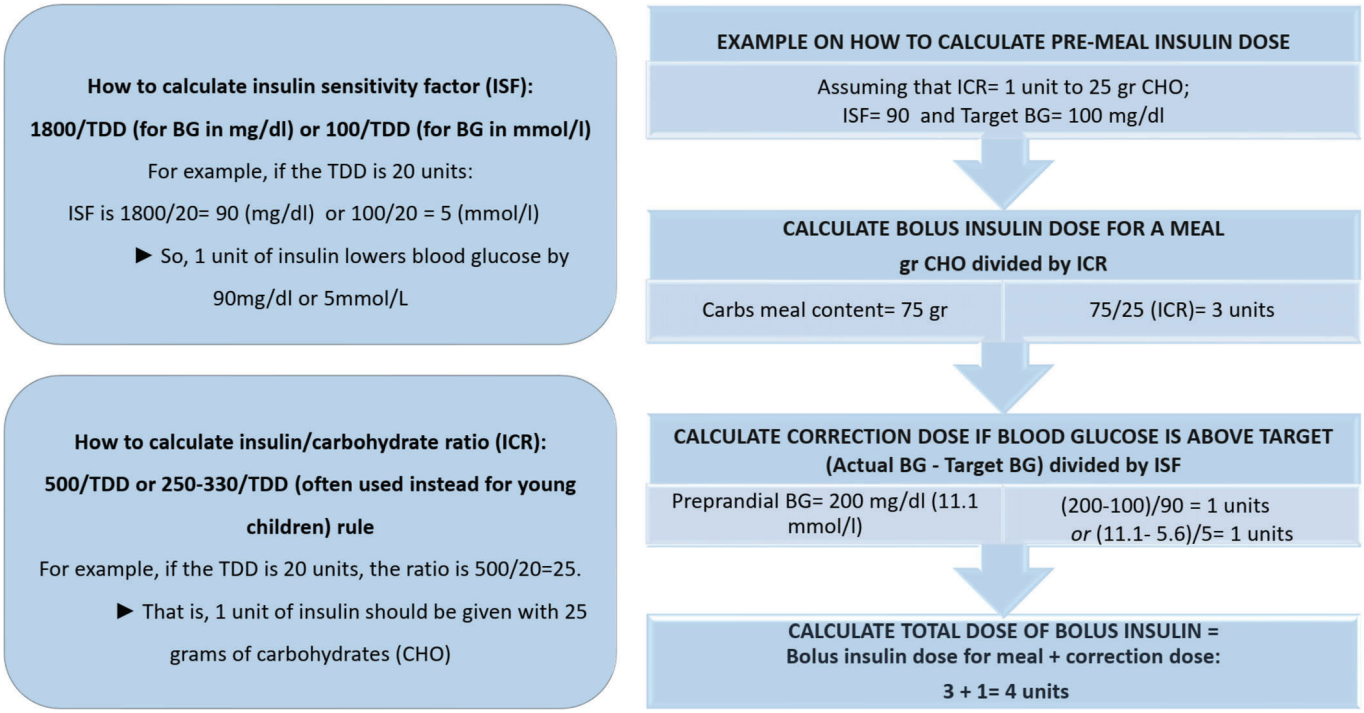

FIGURE 2 Insulin/carbohydrate ratio (ICR) and insulin sensitivity factor (ISF)

are an essential part of the discussion with families. (Figure 2) (see ISPAD 2022 Consensus Guidelines Chapter 9 "Insulin treatment in children and adolescents with diabetes")

- MDI: familiarity with the concepts of carbohydrate counting, insulin to carbohydrate ratio and insulin sensitivity (correction) factors need to be reinforced and reviewed at every visit. More recently, the use of Application (Apps) based bolus calculators has proliferated and are widely and freely available. Adoption of a consistent system by the diabetes team helps to implement and educate about the use such systems.
- Pump therapy: CSII, sensor augmented CSII and hybrid closed loop systems. Several insulin pump (CSII) delivery system platforms are commercially available. Recently the use of hybrid closed loop systems has become more widespread (see ISPAD 2022 Consensus Guidelines Chapter 16 "Technology: Glucose monitoring"; and Chapter 17 "Technology: Insulin Delivery"). Regardless of the specific pump being used, review of "back up" basal rates should occur regularly, particularly in adolescents during rapid pubertal growth. Optimization of insulin to carbohydrate ratios, insulin sensitivity (correction) factors and glucose targets should also occur at each visit in order to optimize algorithm adjustments. Disconnection doses and management of pump failure should be reviewed at each visit to ensure safety and clear procedures are in place in the event of device failure.

5.4.3 | General health and well-being

- History of intercurrent health problems such as infections, enuresis/nocturia, diabetes-related emergency and hospital/emergency department visits, and other pediatric and developmental problems).
- Review of all current medications and supplements including medications from alternative medicine sources, and herbal preparations.
- Systems review with particular attention to symptoms relevant to associated comorbid conditions. In the presence of symptoms or signs, given the predisposition to autoimmune conditions, additional evaluation may be indicated (coeliac disease, autoimmune thyroiditis, adrenal insufficiency).
- New health conditions, including disordered eating behaviors and/or changes in dietary preferences (e.g., adopting a vegan or very low carbohydrate, ketogenic diet).
- Changes in developmental performance, education (particularly school absences or behavioral problems), leisure and sport activities, and psychosocial status.

5.4.4 | Physical examination

- Height, weight, body mass index (BMI) and pubertal status (data recorded and tracked on appropriate growth charts, on which mid-parental height is marked). Weight status can give a general indication of glycemic management, with weight loss and/ or delayed puberty suggesting poor glycemic management.
- Blood pressure with reference to age-appropriate normal levels.
- Oral mucosa and dentition (for dental caries, gingivitis)
- Thyroid gland, cardiac, and abdominal (for hepatomegaly) examinations, feet examination (for corns, ingrown toenails and other lesions) as well as neurological function test (e.g., light touch, vibration sense).

TABLE 1 Screening and prevention guidelines for routine pediatric and adolescent diabetes visits.

	Evaluation	Type 1 diabetes	Type 2 diabetes
Glycemic Management	HbA1c	Quarterly at each visit	
	Glucose values from meter, log, or CGM AGP report for TIR, TBR, TAR	At each visit and in between visits as needed for insulin dose adjustments	
Cardiovascular risk factors	Blood pressure	Every visit	
	Smoking status	Every visit Discourage smoking in youth who do not smoke and encourage smoking cessation in those who do	
	Lipids	Begin ≥11 years; if normal results are obtained; repeat every 3 years.	Begin after glycaemia control or after 3 months of diagnosis; repeat annually
Microvascular complications	Kidney disease: urine albumin: creatinine ratio Retinopathy: dilated eye exam Neuropathy: comprehensive foot exam	Start at puberty or from age 11 years, whichever is earlier, after 2–5 years diabetes duration; repeat annually for kidney disease and neuropathy; every 2–3 years for retinopathy	Begin at diagnosis; repeat annually
Autoimmune screening	Thyroid function: TSH, total or free T4 and thyroid autoantibodies	At or near diagnosis; Every 2 years: TSH (sooner if positive thyroid autoantibodies at diagnosis or with symptoms)	N/A
	Celiac screening (TTG-IgA, if IgA normal)	At or near diagnosis; repeat at 2–5 years intervals (sooner if symptomatic or first degree relative with celiac disease)	N/A
	Addison's disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis	As clinically indicated	N/A
Psychosocial screening	Diabetes distress, depression, disordered eating	Begin shortly after diagnosis; routinely (at least annually)	
Anticipatory guidance	Pre-conception counseling, risk-taking behaviors, transition to adult care	Pre-conception counseling for girls of childbearing potential. Discussion about risk-taking behaviors and preparation for transition to adult care can begin in early adolescence and be revisited at least annually	

- Skin, particularly at the insulin administration and glucose monitoring sites, catheter insertion, for evidence of lipohypertrophy, lipoatrophy, infection or skin reactions to adhesives used for sensors and patch pumps. Providers should reinforce the need for rotation of sites for injection, catheter or sensor. Also note presence of acanthosis nigricans, suggestive of insulin resistance, and in girls, of acne or hirsutism, which may be indicative of polycystic ovarian syndrome.

5.4.5 | Laboratory assessment, particularly HbA1c every 3 months

5.5 | Annual review visits

It is good practice to provide an annual review, which includes the above-described routine outpatient assessment and screening for complications as per guidelines in *ISPAD 2022 Consensus Guidelines Chapter 18 on Microvascular and macrovascular complications in children and adolescents* and summarized in Table 1. The main components of the annual review visit are:

- Expanded physical development with particular emphasis on growth and pubertal development.
- Additional diabetes self-management assessment (e.g., exercise, nutrition and sick-day rules)
- Any new pertinent family history (e.g., new diabetes or other endocrine diagnoses, cardiovascular events/diagnosis).
- Discuss new aspects of diabetes management including diabetes technology
- Consider expanded review of the nutritional plan and dietary management by a dietitian. Parents may be encouraged to bring a food diary recording the last few days' diet to inform the consultation about individualized dietary advice.
- Consider expanded review of physical activity and insulin dose adjustments made to manage exercise.

- Psychosocial assessment that includes screening for depression and disordered eating, household structure (e.g., single vs. two-parent, joint families, sibling issues, household stability, marital stress, parental support), bullying or discrimination at the home, school or workplace.
- Assessment by a psychologist or social worker of the family's and child's adjustment to diabetes and age-appropriate transfer of responsibility for self-care to the older child/adolescent.
- Determination of barriers to successful diabetes management including needle phobia, fear of hypoglycemia (parent and child), and financial challenges (see section below)
- Education concerning the need for routine dental care. Suboptimal glycemic management in children and adolescents has been associated with higher salivary glucose levels and more dental caries.[29]
- For adolescents, guidance around safe driving, effects of tobacco, alcohol, marijuana and other substances on glycaemia and long-term health, sex, contraception and preconception counseling. It is appropriate to request parents/caregivers to wait in another room so that these topics can be discussed privately with the adolescent, and to allow the adolescent an opportunity to practice speaking directly to their provider.
- For adolescents and young adults, preparation for transition
- Assessment of understanding of risks for complications and care plans to minimize these risks.
- Screening for co-morbidities and complications. (see Table 1). This includes screening at regular intervals for thyroid dysfunction and celiac disease in asymptomatic children. In some settings, consider obtaining a hemoglobin or hematocrit, as anemia is common and could be nutritional, pernicious anemia, associated with hypothyroidism or celiac disease, or due to menorrhagia. In the presence of additional risk factors, such as family history of dyslipidemia, additional testing and/or intervention may be indicated. (see *ISPAD 2022 Consensus Guidelines Chapter 19 on "Other complications and associated conditions in children and adolescents with type 1 diabetes"*).

6 | OUTCOMES OF OUTPATIENT CARE

The outcome of each visit should include:

- An individualized plan of diabetes care that includes:
  i. Updated specific insulin-to-carbohydrate ratio and insulin sensitivity (correction) factor for insulin dose calculations and BGM targets
  ii. Particular needs of each child/ adolescent and family to optimize the child's diabetes outcomes (e.g., exercise, nutrition, sick days management)
- A written copy of the plan is provided to the family after the visit, including results of HbA1c measurement (including individual HbA1c target) and screening tests for comorbidities/complications.
- Identification of behavioral goals for the upcoming interval. Motivational discussion including the family's and child's understanding of general treatment goals and an understanding of the medical rationale behind these, for example, good glycemic management is associated with better quality of life and lower risk of microvascular and macrovascular complications. Because children and adolescents are insufficiently cognitively mature to be concerned about health problems in the distant future, emphasis on immediate benefits of good control (feeling better, improved academic and physical performance) may more effectively drive behavioral change.

7 | TYPE 2 DIABETES

7.1 | Structure of care

Management goals include education for diabetes self-management, normalization of glycaemia while minimizing hypoglycemia, weight management, dietary changes, increase in physical activity and exercise capacity and control of comorbidities and complications, including hypertension, dyslipidemia, nephropathy, sleep disorders, and hepatic steatosis.

Education should be delivered by team members with expertise and knowledge of the unique dietary, exercise, and psychological needs of youth with T2D. The education and treatment team for T2D ideally should include a pediatric diabetologist, nutritionist, psychologist and/or social worker, and exercise physiologist. Education in T2D places greater emphasis on healthy lifestyle habits including behavioral, dietary and physical activity changes than is generally required for T1D, and should be provided in a culturally sensitive and age-appropriate manner.

Lifestyle change is the cornerstone of treatment of T2D and clinicians should initiate a lifestyle modification program for children and adolescents at the time of diagnosis of T2D.[30] The interventions include promoting a healthy lifestyle through behavior change, including nutrition, exercise training, weight management, and smoking cessation.

The entire family will need education to understand the principles of T2D management and the critical importance of lifestyle changes for the entire family to successfully manage a youth with T2D.

7.2 | Processes and content of care of T2D

The aims of therapy in youth onset T2D are to improve glycaemia, prevent acute and chronic complications, improve insulin sensitivity and endogenous insulin secretion, restore normal glucagon and incretin physiology, and provide exogenous insulin when necessary. The choice of therapeutic approach should also consider the effect on comorbidities and cardiovascular risk.

7.2.1 | At onset

- The importance of providing a good start with clear, positive messages, support, and advice, cannot be overemphasized. As for T1D, easy access (24 h a day) for rapid diagnosis and initiation of treatment with availability of written protocols, provision of practical

care guidance at diagnosis, and creating a partnership between the care providers and the child and family allowing for shared decision-making.
- Providing psychosocial support for the child and family, assessing resources and potential barriers to adjustment to the diabetes diagnosis are some of the measures that the diabetes team should also initiate.
- Written and/or pictorial age-appropriate materials should be provided in a format (e.g., paper pamphlets, booklets, electronic versions) and language the family understands. Unfortunately, such material is not readily available for children with T2D compared to T1D. Some of the materials are available at TODAY public website (portal.bsc.gwu.edu/web/today) and as an ADA program called Be Healthy TODAY; Be Healthy for Life (http://www.diabetes.org/living-with-diabetes/parents-and-kids/childrenand-type-2/)
- Initial treatment of youth with T2D should include metformin and/or insulin alone or in combination. The specifics of the initial treatment modality are determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis (*see ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes*).

7.2.2 | Subsequent management of T2D

- The goal of initial treatment should be to attain an HbA1c of less than 7.0% (53 mmol/mol) and in some situations <6.5% (48 mmol/mol).[31] This can usually be accomplished with metformin and basal insulin, alone or in combination. Use of other oral or injected agents known to be effective in adults with T2D may be beneficial for youth with T2D in addition to, or instead of, metformin and insulin. Liraglutide has been shown to be effective and safe for use in adolescents with T2D aged 10–17 years and has been approved for use since June 2019.[32] (*Please refer ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes*)
- Blood glucose monitoring should be individualized, with a frequency based on specific treatment plan, degree of glycemic management and available resources. More frequent monitoring is required during acute illness or when symptoms of hyper- or hypoglycemia occur. HbA1c concentration should be determined every 3 months.

Literature to support the use of CGM in youth onset T2D is limited.[33] In the research setting, CGM has also been used as a tool for studying potential differences in the causes of insulin resistance in T2D youth, with CGM-detected hyperglycemia being correlated with increased insulin resistance.[34] Given the greater burden of disease in youth with T2D, further studies are required to identify whether intermittent use of CGM may lead to glycemic improvements and how best to use the device (who may benefit, how often to prescribe and when) to inform therapeutic recommendations in this age group.

7.2.3 | Ongoing diabetes care

- Similar to T1D, the process of ambulatory care for children and youth with T2D includes outpatient follow-up every 3 months and an annual review of care (Table 1). C (*see ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes*)

8 | GLUCOSE MONITORING TECHNOLOGIES IN THE AMBULATORY CARE

8.1 | Practical approach to CGM users and diabetes teams

CGM should be considered for all children with T1D who are on intensive insulin therapy. CGM (rtCGM and isCGM devices, e.g., Freestyle Libre) offer significant advantages over fingerpick BGM. rtCGM should be worn nearly continuously and isCGM should be scanned at least once every 8 h, and more frequently for T1D, in order to use the information well. All CGMs can provide auditory and vibratory alerts when glucose levels exceed or are predicted to exceed high or low pre-selected thresholds, or when glucose levels rapidly rise or fall. These alert settings should be discussed, as unnecessarily tight settings may lead to excessive alarms, leading to alarm fatigue and/or anxiety for children or their caregivers. CGM systems display trend arrows in addition to glucose values. Insulin dosing can be anticipatorily adjusted based on the direction and angle of the arrow, which indicate rate of change. Earlier approaches included increasing or decreasing insulin doses by 10%–20% based on how quickly glucose levels were changing.[35] Newer guidance suggests a specific number of units to increase or decrease based on the individual person's correction factor.[36] While these algorithms may be helpful for some children and families, it is unknown how much this improves glycemic management in children.

Integration of CGM into diabetes care requires an additional level of education, as well as time and effort from the child/adolescent, family, and diabetes care team. Data from CGM systems can greatly enhance the usefulness of the ambulatory care visit. Glucose monitoring device data (either from BGM meters or CGM meters) can be downloaded onto the family's home computer or uploaded to the manufacturer's web platform for family review and for transmission electronically to the diabetes care team before routine ambulatory care visits or when families require advice on management. This facilitates the contact between the family and the diabetes care team, allowing for an effective teleconsultation and promoting "shared decision-making".

Most CGM systems have similar versions of the AGP, which is a standardized glucose report that allows for visualization of daily curves of glucose, median (50%) glucose values and percentage of TIR, time below range (TBR) and time above range (TAR) for the reported period (Figure 3). Clinicians should focus on patterns of glycaemia, and less about single days. It is recommended that diabetes clinicians review 14 days of data for adequate decision-making,[37] which can either be done ahead of time if the person with diabetes downloads their device at home, or can be done at the time of the clinical visit.

The CGM data should be reviewed in consultation with the family to promote a shared decision-making approach and a learning opportunity for the family on how to interpret data themselves.

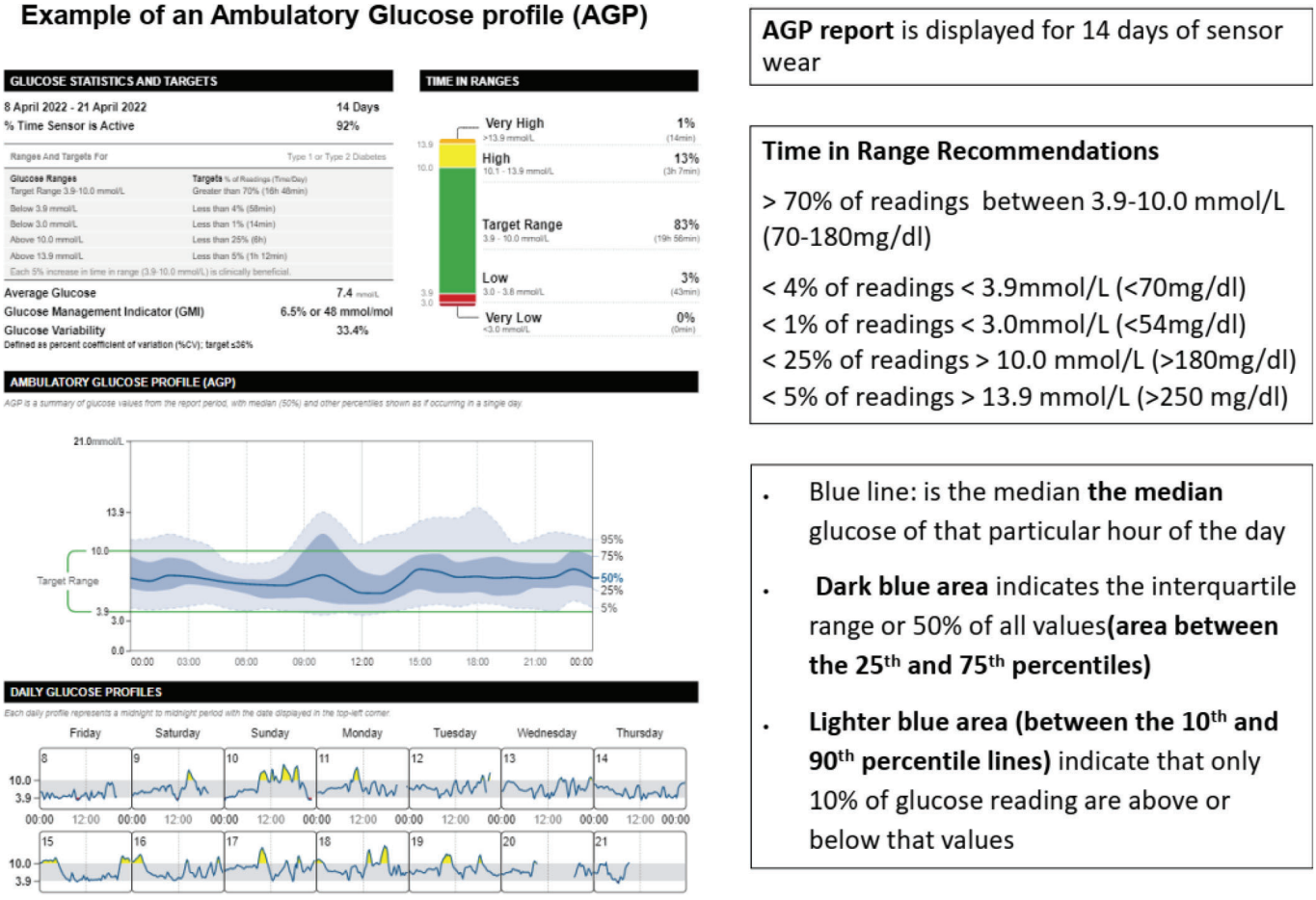

FIGURE 3 Ambulatory glucose profile (AGP)

Typically, patterns of hypoglycemia should be addressed first with insulin dosing adjustments or behavioral instruction (counting carbohydrates, timing of insulin doses). Thereafter, patterns of hyperglycemia should be evaluated, and potential causes identified and addressed. In general, clinicians should consider making 1 or 2 dosing or behavioral changes at a time, as too many changes may confuse the family or lead to new unintentional effects on glucose patterns.

(*Please also refer to ISPAD 2022 Consensus Guidelines Chapter 16* "*Technology: Glucose monitoring*").

9 | TELEMEDICINE AND TELEHEALTH

Telemedicine and telehealth can be described as the use of telecommunications to deliver health services, including interactive, consultative, and diagnostic services.[38,39] The most used approaches are virtual visits via video, telephone, or live chat. Telehealth also includes chat-based interactions to transmit health data to healthcare providers to review and deliver a consultation, diagnosis, or treatment plan.[39] Other approaches are remote monitoring and technology-enabled modalities, for example, physician-to-physician consultation and diabetes education to the families.[39]

9.1 | Evidence for feasibility and positive results

Diabetes is well-suited for telemedicine given that the individual's treatment data can be recorded and shared electronically. Recent studies have shown that video consultation is feasible for diabetes clinic visits[40–42] and psychosocial counseling in young adults with diabetes[43] (Figure 4A). The care concept of the diabetes clinics in the Netherlands, for example, has shown for many years how in-person care for children supplemented by multiple contacts via video, telephone, and email can improve the outcome of children with diabetes.[44] Some qualitative studies[45,46] have reported high levels of satisfaction with telemedicine use among study participants and diabetes care team members, as telemedicine visits can help to overcome barriers related to time and travel distance and offer increased flexibility, feeling of security and more frequent appointments for families. Nevertheless, the level of telemedicine that can be achieved is highly dependent on the infrastructure available and affordability of smartphone/internet technology.

Historically, ambulatory diabetes care has taken place primarily as face-to-face consultations in a diabetes outpatient clinic. However, the organizational design of ambulatory care for children and adolescents with diabetes depends on many factors, including the ratio of diabetes providers for the number of children requiring care in a region and the size of the catchment area. Depending on

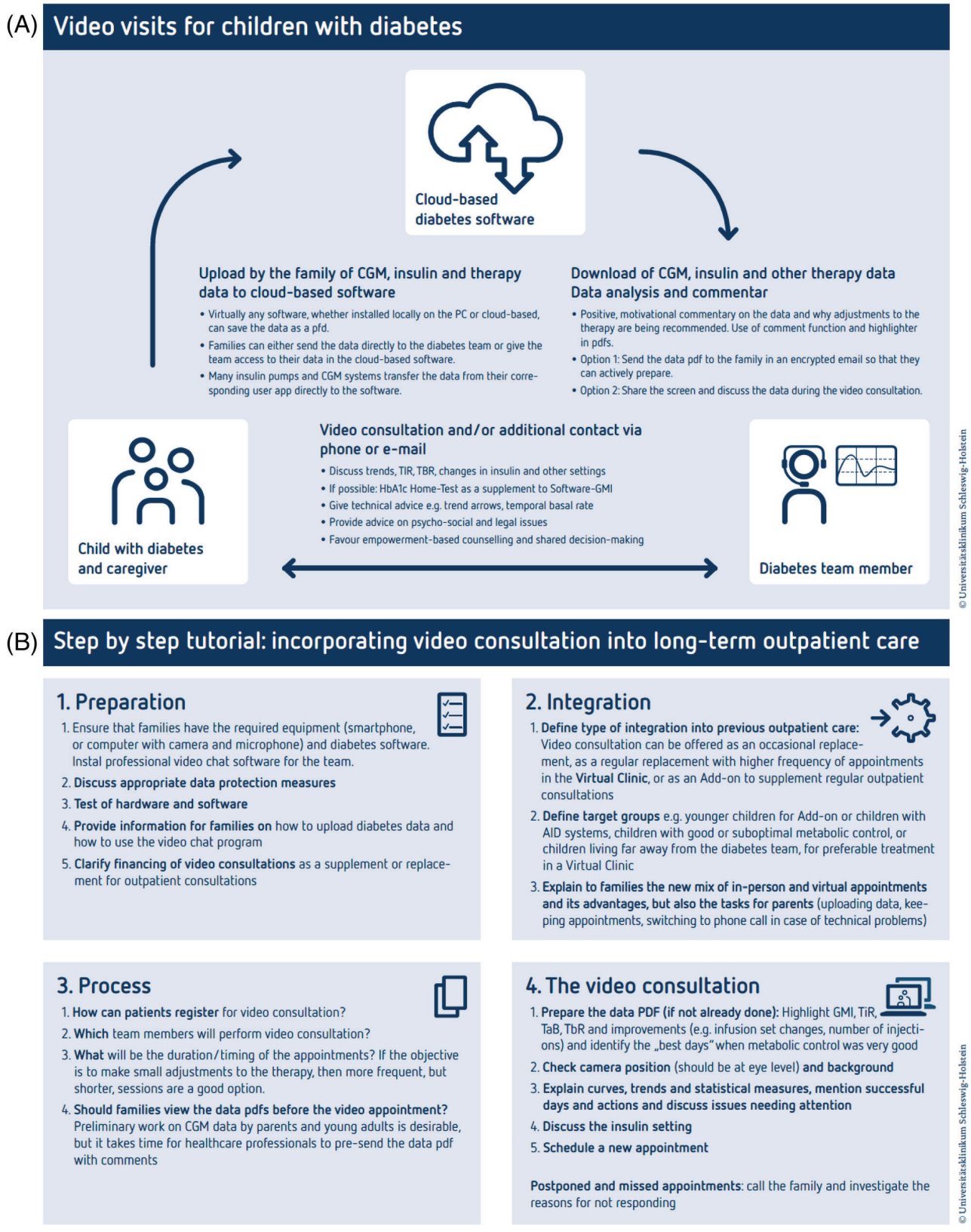

FIGURE 4 (A) Video visits in detail. (B) Video-consultation step by step

the clinic resources and the individual patient's circumstances, it may not always be possible for each individual to achieve the minimum of one in-person visit with the diabetes care team every 3 months.

Telemedicine may provide an opportunity to explore the promotion of equitable care; however, limited access to hardware and software required for video consultations may conversely exacerbate inequities. Taking into account available staff and time resources, it

may also be important to consider whether more frequent but shorter video consultations may allow for better use of existing resources.

9.2 | Two models of telemedicine and telehealth

A typical synchronous (live and interactive) video consultation can offer a virtual environment that is comparable to the outpatient clinic experience through image and audio transmission. The prerequisite for effective video consultation is the transmission and joint viewing of data that include BGM or CGM, as well as information about insulin administration and meals. The storage and graphical presentation of CGM, insulin pump, insulin pen and other data in cloud-based software has made virtual review of therapy data feasible before, during, and after a video consultation. In comparison, asynchronous telemedicine is time-delayed communication, often via email or an electronic medical record portal, between health care providers and persons with diabetes. People with diabetes and their families can contact their care team between clinic visits and then receive feedback in a defined time window.

9.3 | Requirements for implementation of telemedicine

Appropriate staffing models to support video consultations and processes of care to support billing and prescription issues for telemedicine visits need to be clarified and established. This could involve both information technology (IT) support as part of the team and/or team training in technology literacy. Interventions and challenges for restructuring of a diabetes outpatient clinic to successfully include telemedicine and video consultation were assessed especially during the COVID-19 pandemic.[23,47,48] A first important step is to ensure that individuals with diabetes can actively upload their data to a diabetes software and receive technical help, if necessary. Passive data upload and sharing may be available once an app has been linked to the software account. It will be necessary to revise the outpatient care workflows, provide video contacts, and redistribute roles and responsibilities (Figure 4B). To enhance the efficiency of telemedicine, it will be important to overcome the issue of interoperability of the different software solutions, which often do not allow data from different medical devices to be merged.

An advantage of telemedicine is the use of mobile health products (e.g., apps), emails or short text messages to allow extra contacts with families. In the past few years, telemedicine has proven to be feasible for diabetic retinopathy screening using digital photographs of the fundus, which are forwarded and analyzed by a distant eye-care specialist/ophthalmologist. In a meta-analysis, the accuracy of telemedicine retinopathy screening was high.[49] In a recent study, the use of a non-mydriatic camera in the diabetes outpatient clinic has been a suitable option to implement retinopathy screening recommendations in the pediatric outpatient appointment.[50]

Telemedicine services can be an excellent addition to the ongoing outpatient care of children and adolescents with diabetes, by providing an increased frequency of counseling contacts and various additional modes of contact with or access to online diabetes education or expert advice, when needed (Figure S1).

As a result, telemedicine can play an important role in improving access to health care, if a family is equipped with internet access and the requisite diabetes technology and software to record data and share data.

10 | TRANSITION TO ADULT CARE

T1D is commonly diagnosed in childhood but requires lifelong medical care involving both pediatric and adult healthcare systems.[51,52] Planned transition between pediatric and adult health care is a purposeful process over time[53] distinguished from transfer of care, which is a discrete point at which the provider or care setting changes. Both transition preparation and transfer between health systems occur in parallel with the broader developmental task of moving from adolescence to adulthood. Emerging adulthood (late teens through mid-twenties) is recognized as an interval marked by increasing independence and exploration of educational, vocational, social, and financial challenges and opportunities.[54] For emerging adults with diabetes, this developmental stage is often also associated with increasing responsibility for self-management as parental involvement in diabetes care and oversight decreases.[55] Emerging adults may also have a developmentally normative sense of invulnerability, where one discounts risk to future health.[56] Therefore, even though transition is an expected process as adolescents age out of pediatric care, the challenge of integrating increased responsibility of diabetes management occurs in the broader context of competing life priorities, which may contribute to lapses in care and deterioration of glycemic management often observed in this population.[57–60]

Reports from centers in different countries, including those with universal health insurance systems, demonstrate that between 25% and 65% of young adults experience gaps between pediatric and adult diabetes care for significant periods of time[61–63] and express dissatisfaction with the transition experience.[64–66] Adverse diabetes-related outcomes, including suboptimal glycemic targets, increased diabetes-related hospitalizations post-transfer, emergence of chronic diabetes complications and premature mortality have been widely reported.[67–71]

In response, clinical guidelines and a growing body of literature recognize the significance of planned transition from pediatric settings to adult receivership models for emerging adults with diabetes to mitigate the risk of adverse outcomes.[51,52] Anticipatory guidance and identification of modifiable factors, such as transition readiness, self-management skills and psychosocial supports, can promote higher levels of success as indicated by individual-reported satisfaction with care,[58,72,73] effective self-management post transfer, and decreased gaps in care.[74,75] .Discussion about transition to another care team or diabetes care provider at multiple visits before transfer occurs helps

young people prepare for transition.[76] In addition, providing counseling on how care and practices may differ in adult clinics may be helpful to teens.[55] Peer mentoring can be effective to share experiences and organize ways to overcome social barriers to diabetes care that may not be addressed in a medical context.[77]

A 2011 joint consensus statement,[78] along with related resources from Got Transition/Center for Health Care Transition Improvement (www.gottransition.org), set forth specific health care system recommendations and guidelines for planning the transition from pediatric to adult care that include establishing: (1) clinic transition policy; (2) mechanism for tracking persons with diabetes; (3) readiness assessment to identify individual-specific health care needs; (4) longitudinal transition planning; (5) facilitated transfer of care process; and (6) successful transfer completion confirmation. In parallel, recommendations for successful adult receivership include communication between providers, reassessment of knowledge and skills after transfer to adult care, establishing new trusting relationships, addressing psychosocial needs, and a team-based approach.[79,80] A joint effort sponsored by several organizations including ISPAD provides a tool kit of ready to use resources for transition preparation and successful transfer of care available online: (https://www.endocrine.org/improving-practice/transitions#t1d).

There are methodological challenges to systematically evaluate the impact of transition interventions and compare outcomes, based on heterogenous models of pediatric and adult care (Figure 5A). The age and process of transfer to an adult clinic varies by location and health care delivery system, and is influenced by local practices and resources, young people with diabetes and family preferences, and national policies. Descriptive reports of transition programs, systematic reviews of the literature, and clinical trials[81–85] provide insights into existing models and evidence. There are several reported processes for transition between pediatric and adult care, outlined in Figure 5B.

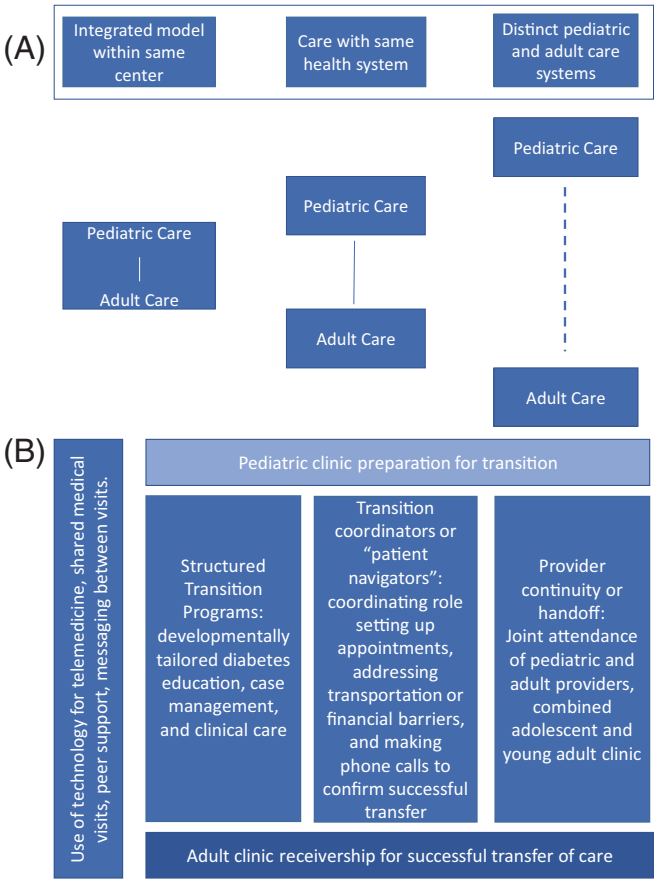

FIGURE 5 (A) Transition models to adult care: Transition models vary in physical proximity, sharing of medical records, and care providers (as indicated by distance and solid or dotted lines in model). Strategies for building connections between pediatric and adult diabetes providers needs to be tailored to local contexts.
(B) Transition process to adult care

- Structured transition programs that include developmentally tailored diabetes education, case management, and clinical care have demonstrated proof of concept in improving glycemic outcomes and health care utilization among young adults previously with a history of or risk for lapses in care.[83–87]
- Programs featuring transition coordinators, or "patient navigators" decrease post-transition gaps and improve post-transition clinic attendance and have reduced DKA rates. The role of navigator may be a community health coach, social worker, or diabetes nurse, whose role is to coordinate setting up appointments, address transportation or financial barriers, and make phone calls to confirm successful transfer.[88–91]
- There are established models that provide case management for the adolescent during a transition process that lasts at least 1 year (www.btp-ev.de).[92]
- Physician continuity between pediatric and adult health care systems can provide a level of familiarity to ease changes in health care settings. Joint attendance of pediatric and adult diabetes care providers at the last pediatric clinic visit and first adult clinic appointment may be beneficial, although this is not always feasible. Alternatively, a combined adolescent/young adult clinic with both pediatric and adult diabetes specialists has been proposed as an optimal model of transition to adult care.[93–95]
- Innovative uses of technology including telemedicine and shared medical appointments can simultaneously reduce barriers to in-person visits and provide peer support.[96–98] Web-based and text messaging interventions have also been used to engage adolescents with chronic conditions between visits.[99,100] As COVID-19 has catalyzed the use of telemedicine, uptake of video telehealth visits has been increasingly tested in the setting of adolescent care.
- Adult providers play an essential role in caring for emerging adults with diabetes by receiving them from pediatric care and maintaining health throughout the lifespan. Adult receivership practices should be in place to facilitate ongoing education, clinical support, and promotion of self-management initiated in pediatric care.[79,80]

In summary, when moving between pediatric and adult health systems, emerging adults have to balance the demands of self-management with competing life priorities, which contribute to a risk for deterioration of glycemic management with associated increased

mortality and morbidity. Based on available evidence and clinical recommendations, a planned, structured transition approach is multi-faceted with elements of longitudinal preparation in pediatric care, active engagement by persons with diabetes and their families in readiness assessments, psychosocial evaluation and interventions, peer support, health navigation guidance, communication between providers, and adult receivership clinics. There is an ongoing need for consensus on meaningful outcome measures to support further rigorous evaluation of intervention studies. In the interim, clinics are encouraged to utilize available free resources to promote an organized approach to transition within the structure of their specific local health systems.

11 | BARRIERS TO OPTIMAL CARE

There are many potential barriers to delivering optimal ambulatory diabetes care, which can be broadly categorized as those related to (Table S1):

i. The organization and infrastructure of health care services, including the accessibility, availability, and affordability of care. Barriers related to infrastructure of care include the distance the individual with diabetes must travel to a diabetes center, inconvenient clinic appointment times, restricted reimbursement, and the shortage and time constraints of physicians trained in diabetes management.[101,102] Potential solutions to accessibility/availability barriers are to offer local diabetes clinic options or, in cases where organizing smaller diabetes centers or regular outreach clinics is not feasible, training local primary care physicians, implementing a shared electronic medical record to track the child's care and identify "red flags" that might impact motivation and clinic visit attendance. Virtual hub-and-spoke networks can be organized in order to disseminate knowledge in underserved areas and support primary care physicians.[103,104] The use of telemedicine provides a potential practical solution to overcome the barriers related to travel and the absence of local expertise in diabetes management.[23,105] Where affordability of care is the main barrier, efforts should focus on advocacy for reimbursement, as well as promoting collaborations between local/national government agencies and diabetes advocacy groups.
ii. Social determinants of health, including a) socioeconomic status and related housing and food insecurity, as well as limited access to social security, b) educational status and literacy, c) neighborhood and built environment that can provide access to healthy eating and space for exercise, and d) determinants of social context and cohesion, such as incarceration, domestic violence, substance abuse, as well as discrimination and stigma. Minority status, a crucial social determinant of health that encompasses most of these factors, is discussed separately.[106,107] These factors have been consistently correlated with suboptimal glycemic outcomes and clinic attendance, highlighting the importance of focusing on these factors.[108,109]

Screening for social determinants of health could help identify issues affecting diabetes management and overcome communication gaps between diabetes care providers and young people with diabetes and their families.[110,111] Stigma is perceived in 36–78% of people with diabetes even in socially sensitive societies.[112] Integration and acceptance should begin in the school setting and be supported at the community level through educational campaigns.Diabetes care teams should consult resources on social determinants of health that are currently available from various organizations[107] and assist families to use community services if social needs are identified.

iii. Psychological factors/individual perceptions and needs that pertain to the acceptability of care. The perception of the child and their family regarding the burden of diabetes management in their everyday life should be acknowledged. Some families may underestimate the usefulness of structured educational programs, regular clinic attendance or even the benefits of efficient self-management and good glycemic management, and they might feel already self-confident and empowered, even if diabetes is not optimally managed.[113] It is crucial that the diabetes team identify and address these issues,[114,115] by providing problem-oriented interactive education that may include integrating technology, revisiting daily routines and treatment options, ensuring mental health support, and restoring communication and balance within the family.[116–119] Language used by the diabetes care team is crucial for building a strong relationship. It should be kept accessible and simple, motivating, compassionate, yet realistic, not judging or shaming and adjusted to the personal preferences of the child with diabetes.[120]

The presence of mental health comorbidities and family conflicts can influence diabetes management as well.[121,122] Available tools should be used to screen for and identify mental health comorbidities and barriers to diabetes self-care.[123–131]

Barriers to incorporate the use of technology in daily diabetes care should also be considered in young people with T1D.[132–134] These may include concerns about (i) increased burden on diabetes management (overwhelming data, difficulties in downloading and data interpretation, alarms, faulty devices); (ii) therapeutic effectiveness of the devices (mistrust of automated decision making technology, inaccuracy of measurements); (iii) physical interference of the devices (adhesion and insertion issues, multiple devices, body image, "public display" of diabetes, interference with daily activities and exercise).[135–137] In some cases, even the diabetes care team can be reluctant to actively introduce technology, being themselves overwhelmed by the extra burden related to its implementation.[138,139] The sustained benefit of the use of technology on metabolic control and quality of life of children, adolescents and young adults with T1D is by itself the most rewarding motivation.

12 | CARE FOR CHILDREN FROM MINORITY GROUPS AND CHILDREN OF RECENT IMMIGRANTS: A PRACTICAL APPROACH

Globalization and migration are great challenges to health care systems. The recent fluxes of immigrants and refugees have changed the characteristics of the populations accessing the healthcare services in

the host countries, requiring changes of the local diabetes care team to address the needs of these people. Data demonstrates that children with diabetes from migrant/minority families have less favorable glycemic outcomes, higher body mass index, less physical activity, lower utilization of technologies and higher frequency of diabetes-related hospitalization than native populations (Table S2).[140,141]

As immigrants and refugees are usually not aware of the health insurance policies and organization of the heath system of their host countries, it must be ensured that children with diabetes have unrestricted access to a safe location to store insulin, glucagon, diabetes management-related consumables, and devices and that instructions are well understood and followed. Key points related to the ambulatory diabetes care of children from minority groups and immigrant populations are:

- Define structured pathways of care for the initial visits.
- Assign a regular provider for each child
- Provide home and school visits, when possible.
- When available, dedicated staff members known as "patient navigators" may help families with T1D through the healthcare system (e.g., set up appointments for doctor visits and medical tests, assist with obtaining financial, legal, and social support if needed).[142,143]
- Licensed interpreters must be used to support the diabetes team in understanding some of the cultural norms. If a licensed interpreter is not available, a non-family member may serve as an interpreter. The child or other family members should only be used as an interpreter if no other option is available.
- Translation of educational material, diabetes management plans, instructions for emergencies, as well as important administrative forms (i.e., informed consent for the use of personal data) in the most common preferred language. If possible, medical certificates that accompany the child should also be translated.[144–146]
- The diabetes team should be aware and familiar with cultural differences that may have an impact on diabetes management. Where available, cultural and language specific materials should be used (i.e., Translation and Cultural Adaptation of the "Barriers to Diabetes Adherence" into Arabic Context, picture-based carbohydrate-counting resource for Somalis, etc.) as well as sensitive toolboxes such as EthnoMed (www.ethnomed.org).[147] Specific guidelines for the management of diabetes during Ramadan or other religious fasting are available and should be discussed with specific families (*See related ISPAD 2022 Consensus Guidelines Chapter 24 on Ramadan and other religions fasting by young people with diabetes*).

12.1 | Racial disparities

It is important to recognize the presence of racial disparities in the provision of ambulatory diabetes care. Studies have shown differences in the receipt of recommended screening for diabetes-related complications and comorbidities, based on race/ethnicity.[148,149] Racial disparities are particularly evident in the use of diabetes technology. These differences cannot be solely attributed to lower socioeconomic status, educational level or health insurance status, but may reflect lack of a culturally sensitive approach and systemic structural racism.[150–152] To overcome these barriers, efforts should be made to actively support the use of technology for all in a trackable and standardized way.

13 | EDUCATION AND LITERACY IN DIABETES TECHNOLOGY

Diabetes technology has evolved rapidly and the number of youths using advanced diabetes technologies has increased substantially in the past decade. Youth with diabetes are routinely using CGM, smart insulin pens, CSII using insulin pumps, and AID to support glucose monitoring and insulin delivery for their day-to-day management. Despite the rapid integration of diabetes technology into pediatric diabetes care, there continue to be multiple barriers to the uptake, use, and accessibility of diabetes technologies for youth with diabetes. Thus, robust diabetes education, device training, and follow-up of children and families are essential to minimize device discontinuation and maximize proper device use to help achieve target glycemic outcomes.

Health care teams play an important role in setting realistic expectations for the youth and family when starting on any new diabetes technology and ensuring an understanding of what devices can and cannot do to support diabetes management.[153] Technology selection must be appropriate for the youth with diabetes. While device companies offer online tutorials and training videos, as well as written materials on their use, structured education delivered by the care team can provide youth and families with practical guidance to support the successful adoption and use of technologies.

Historically, structured, person-centered, and empowerment-based education programs for diabetes technology use have been delivered mostly in-person by a certified diabetes specialist. With the expansion of telehealth services during the COVID-19 pandemic, virtual training sessions to start diabetes technology have been shown to be feasible since CGM and insulin pump data can be uploaded from home and accessed remotely by care teams.[154–157]

Since multiple caregivers are generally involved in a child's care (e.g., babysitters, daycare providers, school nurses, teachers), education and support must extend beyond the youth and family in pediatric diabetes care. In addition, routine clinic visits should be used to re-evaluate the benefit being achieved by and the adequacy of use of the diabetes technology by the medical provider.[158] If there is a lack of measurable benefit, or a concern about safe use of the technology, ongoing training and education in the use of diabetes technologies for youth and their families should be provided, especially given that the technologies are constantly being improved and updated. Studies examining re-education of more experienced insulin pump users, showed reduced frequency of hypoglycemic events and slightly improved HbA1c levels.[159]

Deficiencies in literacy and numeracy can make diabetes education and the use of diabetes technology very difficult. Pictorial

materials can be developed to assist with these situations. Innovative measures can be used, such as teaching the mother or child to draw the numbers because they cannot write them, providing pre-marked syringes (wrapped with colored tape to mark the dose), and using color coding to designate doses of insulin based on proximity of glucose reading to target range. Somewhat similar is the problem of multiple languages or dialects as educational and instructional materials may not be available in the local language. Finally, education should be provided in a developmentally appropriate format that meets the behavioral and emotional needs of a growing child and family. To support the incorporation of child-centered language, the act of play can be used to introduce information about diabetes technology in an age-appropriate manner.[160] Given the potential of play-based strategies providing the child with positive experiences related to their ongoing diabetes care and their interactions with the diabetes team, certified child life specialists can be incorporated as members of the multidisciplinary care team.

Health care team members training and supporting the youth and family on the use of diabetes technology must be proficient with all glucose monitoring and insulin delivery technologies available to prescribe to their persons with diabetes. Teams should develop formal standards, which set out the core competencies expected of staff delivering diabetes technology education and care.[161] In addition, to support requisite expertise on the multidisciplinary care team, teams should consider:

- Having at least one staff member with formal training in the use of each diabetes technology device approved for use for their young children with diabetes
- Providing guidance to the entire care team on available systems and their suitability for different types of users
- Offering relevant continued professional development, if available, to the entire care team and encouraging the use of demonstration systems to support understanding of the functionality of advanced diabetes technologies

Applications (apps) for smartphones designed to support diabetes self-management offer an additional tool for supporting diabetes education and self-management. These include apps for tracking data (e.g., blood glucose values, insulin doses, and carbohydrate counting), apps for teaching and training, and food reference databases. While the growth of digital health apps has the potential to offer benefit to youth with diabetes, the available evidence on the safety and effectiveness of mobile health apps for diabetes remains limited.[162] Regardless, given the growing use of diabetes apps, health team members should be knowledgeable about commonly used apps and their strengths and weaknesses. Further, care team members should be comfortable on how to support youth and their families on the use of digital health apps to augment diabetes management, as well as inform them about the privacy risks and steps that can be taken to keep data confidential and secure.

Please also refer to ISPAD 2022 Consensus Guidelines Chapter 16 "Technology: Glucose monitoring"; and Chapter 17 "Technology: Insulin Delivery").

14 | CHILDREN WITH DIABETES AT SCHOOL: HOW TO INTEGRATE DIABETES MANAGEMENT IN A SCHOOL SETTING

Children with diabetes have the same right to participate in education as their peers without diabetes. However, data show they are at higher risk from being excluded from school.[163]

Normalization of day-to-day living and functioning in the school settings for children should be a primary goal of diabetes care. Children spend 40%–50% of their waking hours in school, and much of their socialization skills is learned there.

The outpatient diabetes team should work closely with schools and empower school staff through education and provision of relevant and appropriate information, to confidently look after children with diabetes. The diabetes team should also support the school and family in developing the diabetes management plan and update it as needed.

A designed member of the diabetes team (often a diabetes educator/nurse) should be the point of contact for school staff and be available to provide regular training/support and be contacted should the staff require assistance during school hours.

For additional information see ISPAD 2022 Consensus Guidelines, Chapter 22 "Management and support of children and adolescents with T1D in school".

15 | CHILDREN WITH DIABETES IN ORGANIZED CAMPS

Diabetes camp (or diabetes school camp) is an educational activity developed for children, adolescents and young adults with diabetes, in a setting located outside the hospital. Diabetes camps have been organized since the first half of the 20th century, soon after the introduction of insulin to treat people with diabetes.[164] Diabetes camps provide a typical camping experience of different durations and usually include a variety of activities.[165]

Many local and national diabetes organizations manage residential and day camps for children and adolescents with diabetes. It is estimated that worldwide 15,000–20,000 young people attend diabetes camps annually.[164] Diabetes camps are usually staffed by professionals and volunteers trained in the management of children with diabetes. Please see Box 3 for details of requirements of Diabetes Camps.

Diabetes camps offer children and adolescents the opportunity to enjoy a camping experience in a safe environment and to experience a setting where caring for diabetes is a shared experience with other campers who also have diabetes. During their camp experience, many children learn more about how to care for their diabetes.

Most camps provide some education on diabetes management, either in planned formal sessions or, more commonly, by taking advantage of helping campers "learn by doing" and of "teachable moments" to discuss topics one-on-one or in a group. However, camp staff should understand that the primary goal of camp is to provide an

BOX 3 Camps specializing in children with diabetes should have

- Adequately trained staff
- Presence of a complete diabetes team, including
  - At least 1 physician serving as camp coordinator
  - At least 1 pediatrician/pediatric resident per 10 campers
  - At least 1 nurse per 5 campers
  - At least 1 dietitian and 1 psychologist
  - An adequate number of educators/entertainers for the regular operation of the camp
- Available insulin and consumables to meet children's needs
- Knowledge of insulin dose adjustments (considering an increased level of activity)
- An understanding of how to manage different glucose sensors, pumps and algorithms
- A staff trained to recognize and treat hypoglycemia and ketosis (and decide when referral to a medical facility is necessary)
- A member with knowledge of nutrition, carbohydrate content of meals, and the principles of insulin doses adjusting for variable carbohydrate content of meals
- A plan to maintain a log of each camper's glucose levels and insulin doses
- What is necessary to manage sick day, trauma or initial medical emergency

enjoyable experience for each child and to interact with other children with diabetes in a safe environment.[164,166] Camps can also be valuable venues to test a new technology (CGM, pump, algorithm, drug) in children and adolescents with diabetes in a real-life setting.[167–169] Furthermore, camps can be used to conduct studies in a small group of people, to evaluate different aspects of the disease (such as physical or psychological)[170] or to evaluate a clinical algorithm.[171]

Many national organizations have position statements or guidelines for the care of children with diabetes in a camp setting. These are valuable references and should be reviewed by camp medical directors to ensure that national standards are used.[165]

16 | QUALITY OF CARE, STRUCTURE OF CARE, PROCESSES OF CARE AND OUTCOMES

Despite remarkable advances in pharmacology and diabetes device technology, many people with diabetes continue to experience suboptimal health outcomes.[172,173] Diabetes centers need methods to evaluate and enhance the quality and equity of the services they provide and the outcomes of their management.[174] Given the complexity of diabetes management, a multifaceted approach that integrates psychosocial supports,[11] recognizes contributions of social determinants of health,[175] leverages information science,[176] and application of QI methodology[177] is needed to complement emerging therapeutic modalities for diabetes.

QI methods describe a systematic and continuous approach to accomplish measurable change in a process or outcome of care.[178,179] Reliable implementation of evidence-based care processes, such as uptake of diabetes technology and rates of preventative screening laboratory tests and services, predictably precede improvements in clinical outcome measures such as HbA1c, TIR, severe hypoglycemia, quality of life, and reduced long-term complications of retinopathy or nephropathy.

The impact of features such as composition of diabetes care team, access to care and costs, frequency of visits, type of encounter via telehealth or in-person, community and peer supports on clinical outcomes remains an important topic for health services research in in pediatric diabetes and is an emerging area for further QI efforts. Across categories of structure, process, and outcomes, selection of meaningful measures is essential to the practice of QI to monitor progress and direct interventions. Increasingly, there is recognition of the importance of metrics beyond HbA1c alone to describe salient elements of care delivery, diabetes management, and lived experience.[180–182] Efforts towards inclusion of individual-reported outcomes, collaborating with people with diabetes and families in QI initiatives, addressing social determinants of health, and screening for common comorbidities associated with diabetes offer further opportunities for an even more comprehensive understanding of quality assessment of pediatric diabetes services.

Diabetes registries can be an important tool for population management at individual centers, QI, and benchmarking across collaborative centers.[183] Benchmark reporting that evaluates effectiveness of diabetes care measured against guidelines for standard practices can promote accountability and system wide improvements in diabetes care.[176,184–189] When data transparency through benchmarking is combined with QI methods and open sharing of best practices, it is possible to accelerate and sustain process improvements and measurable changes in outcomes.[190] The international SWEET registry showed worldwide improvement of HbA1c and increased use of diabetes technology associated with twice yearly benchmarking.[191] The Swedish National Pediatric Registry (SWEDIABKIDS) is an example of a national QI collaborative that observed a sustained decrease in mean HbA1c level for children 0–18 years from baseline of 62.6 mmol/mol (7.9%) in 2010 to 56.9 mmol/mol (7.4%) in 2014[192,193] and continues to be a leader in pediatric diabetes outcomes.

Involvement of governments and policy makers facilitates provision of adequate resources that are required for high quality diabetes care. It should be a priority to collect and provide information on cost of care and long-term cost-effectiveness data of optimal care of children with diabetes to governments and health care agencies.

17 | BALANCING COSTS AND BENEFITS IN DIABETES CARE

Diabetes imposes a large economic burden on the individuals, their families, national health systems, and countries,[194,195] which is likely underestimated in low-income and middle-income countries (LMICs), due to the scarcity of representative population-based information and premature deaths before diagnosis. In other areas of the world, these numbers are also underestimated because they do not account for loss of quality of life, loss of productivity as well as burden of care on the families.

Analysis of costs of care is important in helping to determine appropriate recommendations for care and in health policy decision-making.[196] The total health care expenditure for diabetes was estimated to be greater than USD$ 760 billion dollars and equivalent to ~12% of all global health expenditure.[197] It is of great concern that ~80% of all expenditure is associated with treatment of complications, suggesting their prevention could significantly reduce global health costs.[198] There is vast disparity in health spending between regions and countries. In 2019, only 14.8% of global diabetes health expenditure was spent in LMICs, where 41.8% of people with diabetes live.[197] A study in LMICs reported that annual inpatient and medication costs were the most expensive aspects of diabetes care, with a high degree of cost variability. Reported annual inpatient costs ranged from less than US$20 up to more than $1000, and medications alone ranged from less than $20 per year to more than $500.[199] Studies by the International Insulin Foundation found suboptimal access to insulin in seven LMICs, with availability in only 20% of public sector outlets in Mali and Mozambique.[200]

Despite promising downward trends in mortality and disability-adjusted life years (DALY) rates observed over the past three decades, there remains a substantial gap in life expectancy between people with T1D and the general population, even within high-income countries (HICs).[201] In Sweden, Scotland, and Taiwan, T1D resulted in 10.2–17.7 lost life years; this life-expectancy gap is more pronounced among low-income settings with poor access to insulin.[202] A Swedish study showed that higher life expectancy was correlated with lower HbA1c and higher estimated glomerular filtration rate.[203]

The proportion of children with optimized glycemic outcomes (HbA1c <7·5%) was estimated to be 32.4% in HICs, 27.5% in upper-middle-income countries (UMICs), 21.7% in LMICs, and 12.7% in low-income countries (LICs). Notably over the past 15 years, on average about 76.4% children with T1D globally were unable to achieve optimized glycemic outcomes.[204] Hence, an investment in gold standard care particularly during childhood and adolescence should be advocated globally and it is likely to lead to significant economic benefits. Improved glycemic outcomes through adequate education, treatment modalities and regular glucose monitoring can decrease the risk of complications. It is obvious that regular home glucose monitoring is cost effective, decreasing costs of diabetes care by reducing emergencies.

Both rapid- and long-acting analogs have been shown to reduce the frequency of mild and moderate hypoglycemia. Given the reduced incidence of hypoglycemia, newer analogs may be even more cost-effective.[205] However, affordability for individuals remains a challenge in many settings with cumulative markups ranging from 8.7% to 565.8%.[206] In many LMICs, the price of insulin is paid for by the individual or, in some contexts, subsidies are in place. By contrast, in most HICs, various government-funded or health insurance schemes provide some form of financial protection, either ensuring that insulin is provided for free to the individual or, at least, that the person does not bear the full cost.[207]

The most notable change in diabetes management over the past 5–7 years has been the substantial increase in use of CGM which has led to a reduction in HbA1c.[172] The increase in CGM use has been most prominent among young children, giving parents the ability to monitor glucose data remotely. The early adoption of insulin pumps and CGM are associated with less frequent hospital admissions due to diabetes ketoacidosis compared with injection users. Among individuals with diabetes using CGM, HbA1c concentrations were similar among MDI users or insulin pump users.[208]

Studies on CSII versus MDI suggest that CSII modestly lowers HbA1c compared with MDI, but there is insufficient data on other glycemic outcomes. In a study in socially disadvantaged young people living in HICs, despite an overall suboptimal HbA1c, CSII led to some improvement in glycemic outcomes.[209] A large non-randomized prospective study supported the idea of early CSII initiation following T1D diagnosis.[210] However, Blair and colleagues, who compared clinical outcomes and costs associated with CSII versus MDI, concluded that CSII was not clinically superior to MDI when started at diagnosis and was associated with significantly higher costs.[211]

AID systems might offer even better futures for children and young adults living with T1D and could 1 day be available in LMICs.[212] Both inpatient and outpatient trials have indicated that AID are more effective than conventional therapy at achieving higher percentage of time in range, and reduced time in hypoglycemia and hyperglycemia.[213] There are still no data comparing the costs of using different insulin delivery systems.

Although the benefit of insulin analogs, CGM and AID systems are well known, a large proportion of people with diabetes have restricted access to such high-priced treatment modalities.[133] It is important to continually reassess cost-effectiveness of insulin therapies and technologies as advances are made and as outcomes data are collected over longer periods of time. Advocacy for broad access and affordability of optimal therapies is needed to ensure equitable delivery of care.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13417.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Limbert C, Tinti D, Malik F, et al. ISPAD Clinical Practice Consensus Guidelines 2022: The delivery of ambulatory diabetes care to children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(8):1243-1269. doi:10.1111/pedi.13417

Accepted: 11 November 2022
DOI: 10.1111/pedi.13455

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes

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KEYWORDS: adolescents, children, glucose monitoring, glycemic targets, type 1 diabetes

1 | WHAT IS NEW OR DIFFERENT

Inclusion of continuous glucose monitoring (CGM) targets for children, adolescents, and young adults <25 years.

Emphasis on individualized care plans that make use of effective educational strategies to achieve glucose targets that are person-centered and designed to empower young people and caregivers. These plans should incorporate cognitive behavioral techniques that encompass:

- problem-solving
- goal setting
- communication skills
- motivational interviewing
- family conflict resolution
- coping skills, and stress management

Adoption of a unified fingerstick capillary glucose (SMBG) target of between 4 and 10 mmol/L (70–180 mg/dl), which aligns with the

target CGM time in range (TIR), while emphasizing a tighter fasting target range of 4–8 mmol/L (70–144 mg/dl).

Recognition that disparities in the social determinants of health (SDOH) and inequitable access to modern diabetes therapies represent significant barriers to achieving glucose targets and optimizing clinical outcomes. Health stakeholders are responsible for addressing this disparity.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Achieving target glucose levels assessed through CGM, HbA1c, and/or SMBG:
  - Reduces risks of acute and chronic complications of diabetes **A**
  - Minimizes the detrimental effects of hypoglycemia and hyperglycemia on brain development, cognitive function, mood and quality of life **B**
- Target HbA1c for young people with diabetes should be <53 mmol/mol (<7.0%) **A**
  - An HbA1c target of <48 mmol/mol (6.5%) is recommended for the remission phase or early stage 3 diabetes "honeymoon" period and in populations with access to advanced technology combined with a highly skilled specialized health care professional service adept in diabetes education **E**
  - HbA1c assessments are recommended every 3 months **E**
- CGM metrics, recorded over a 14-day period, should have time spent as follows: **B**
  - >70% between 3.9 and 10 mmol/L (70–180 mg/dl)
  - <4%: <3.9 mmol/L (70 mg/dl)
  - <1%: <3.0 mmol/L (54 mg/dl)
  - <25%: >10 mmol/L (180 mg/dl)
  - <5%: >13.9 mmol/L (250 mg/dl)
  - Glycemic variability (coefficient of variation, [%CV]) target ≤36%
- SMBG should be assessed at least 6 times a day for a person with diabetes taking insulin **B**
- Recommended target glucose values are between 4 and 10 mmol (70–180 mg/dl), with a narrower fasting target range of 4–8 mmol/L (70–144 mg/dl). **E**
- Less stringent HbA1c, CGM, or SMBG targets are only advisable when achieving the standard target is assessed as being detrimental to the overall well-being of the person with diabetes or their caregivers. Factors to consider when setting a less stringent target include (but are not limited to):
  - access to insulin analogs, advanced insulin delivery technology (for example automated insulin delivery), supplies needed to regularly check capillary blood glucose levels, or CGM needed to safely achieve targets **E**
  - Underlying significant psychosocial health concerns exacerbated by efforts to achieve target glucose levels **E**
- A multidisciplinary education team should clearly and collectively communicate recommended glycemic targets; sharing the same philosophy and goals and speaking with "one voice" has beneficial effects on glycemic and psychosocial outcomes. **B**
- Individualized care plans are recommended to help a person with diabetes achieve glycemic targets. **E**
- Data collection and between-center benchmarking can improve the proportion of people with diabetes reaching glycemic targets. **B**
- Addressing social determinants of health, and improving access to the healthcare team, insulin, and technologies increases the proportion of people reaching glycemic targets. **A**

3 | THE IMPORTANCE OF SETTING GLYCEMIC TARGETS

Glycemic targets for young people with diabetes are needed as optimizing glycemia reduces short and long-term complications.[1,2] In addition to protecting against micro- and macrovascular complications, of particular importance in pediatrics is the negative association of hypoglycemia and hyperglycemia on cognition and brain structure,[3] especially in individuals with early onset diabetes.[4] Further, the wider impact of diabetes on healthcare systems and health economics is an important driver to target better glycemic outcomes to prevent future complications.[5,6]

Diabetes registries have shown steady improvement in median HbA1c levels in recent decades, yet only a minority of young people attain current glycemic targets.[7] The improvements that have been demonstrated can be attributed to multiple factors, including how healthcare teams set and communicate glycemic targets, improved therapeutics (insulin analogs, CGM), highly skilled and knowledgeable workforce, and, recently, the use of automated insulin delivery systems. Nevertheless, social determinants of health, pediatric diabetes workforce constraints, and access to improved therapeutics remain significant barriers preventing more young people from reaching target glycemia, and further, drives health inequity.[8,9]

Setting glycemic targets has been standard practice for diabetes organizations, including ISPAD, the American Diabetes Association (ADA), and the National Institute of Clinical Excellence (NICE) in the United Kingdom for 20 years, and have been regularly updated when evidence has supported change.[10] For example, when different stakeholders published divergent HbA1c targets, and lower HbA1c targets were shown not to increase the rates of severe hypoglycemia,[11] lower targets were adopted. It is important to recognize that setting targets contributes to improving glycemia as shown by the observation that a combination of setting a lower target HbA1c and consistency among members of teams within centers is associated with lower center HbA1c levels.[11,12] It is essential that target setting is a collaborative discussion with the person with diabetes (including caregivers) and health care professionals. Furthermore, prospective audit activity, involvement in data registries, and clinical benchmarking, including quality improvement implementation, are also associated with overall improvements in glycemic outcomes.[13,14]

Health care professionals and people with diabetes now have a wide array of tools to assess glycemia, including self-monitored capillary blood glucose (SMBG) values, HbA1c, and CGM. While traditionally HbA1c has been the gold standard, there are limitations to

this measurement as discussed later. Correspondingly, with rapidly increasing adoption of CGM, which arguably avoids these limitations, CGM metric reporting has been standardized and CGM metrics are included in this chapter. The recent COVID-19 global pandemic, and increased opportunities for the use of video or phone appointments between a person with diabetes and/or their carer and the health care professional, has highlighted the utility of CGM metrics to assess glycemia when laboratory measurement of $HbA1_c$ level is not available. While disparities also exist for accessing telemedicine including implicit bias, well-developed work plans can expand the population who can benefit from this health delivery method.[15] Nevertheless, not all young people can access CGM and are reliant on SMBG and/or HbA1c measurement. Using all available forms of glycemic data, in combination if available, will give the most accurate account of glycemia to help guide therapy.

Individualized glycemic target setting above the stated HbA1c target has been emphasized in recent consensus statements.[16,17] This was included to address concerns that for some young people with diabetes, particularly in limited resource settings, (see ISPAD 2022 Consensus Guidelines Chapter 25 on Managing Diabetes in children and adolescents in Limited Resource Setting) stringent HbA1c targets may increase the risk of severe hypoglycemia, or cause psychological distress (for the person with diabetes and/or their caregivers) through treatment burden that outweighs the long-term benefit of a lower HbA1c. Although historically lower HbA1c was considered a risk factor for severe hypoglycemia, this association is no longer observed with contemporary intensive management.[18] For example, data registries have demonstrated that the overall incidence of severe hypoglycemia has decreased at the same time overall HbA1c has improved.[19] Access to diabetes technology, including CGM with or without automation of insulin delivery, can further reduce the risk of severe hypoglycemia while making it possible to achieve target glycemia (see ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring, and Chapter 17 Diabetes Technologies: Insulin Delivery). Therefore, outside of limited resource settings, risk of severe hypoglycemia can no longer be justified as a reason for a higher HbA1c target in the majority of cases. However, if setting stringent glycemic targets is considered to have an overall negative impact on psychological wellness (either for the person with diabetes and/or their caregivers), which may include severe anxiety that outweighs the long-term benefit of optimizing glucose values, a higher glycemic target may be appropriate in combination with efforts to address the barriers to healthier glycemia. Other exceptions occur in certain situations, for example, in a person with diabetes and a limited lifespan or neonatal diabetes, and in situations where stringent glycemic targets are unattainable and will add management burden over any improvement in short or long-term morbidity and mortality.

In ISPAD 2022 Consensus Guidelines Chapter 6 on Diabetes Education in Children and Adolescents, we highlight the importance of the multidisciplinary education team sharing the same philosophy and goals and speaking with "one voice," with beneficial effects on metabolic and psychosocial outcomes. Education should be person-centered, with a personalized diabetes educational approach being an integral part of the psychosocial support for young people with diabetes and their families. (See ISPAD 2022 Consensus Guideline Chapter 15 on Psychological Care of children and adolescents with type 1 diabetes). Therefore, for the majority of young people with diabetes, the priority of the multidisciplinary team is to develop (in consultation with the person with diabetes and their caregivers) an individualized care plan to achieve the ISPAD recommended targets, rather than individualizing the glycemic target itself.

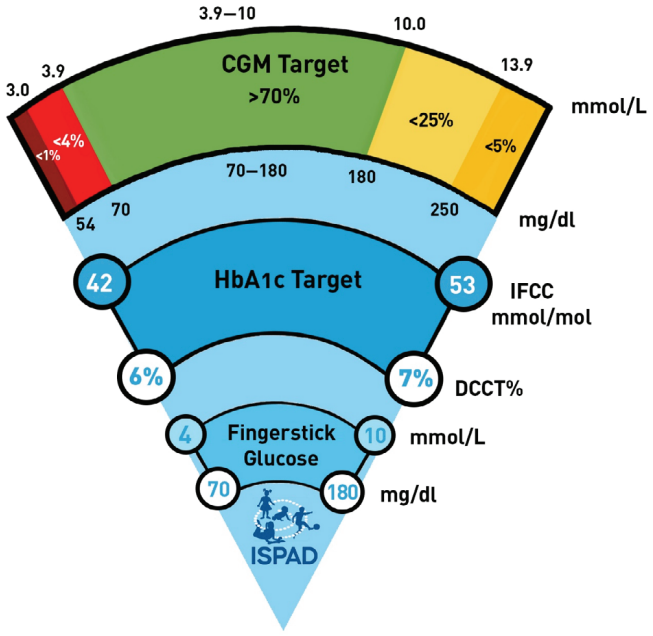

FIGURE 1 Glycemic targets are dependent on the measures available; finger stick capillary glucose (SMBG) levels, HbA1c, and CGM values. The term "finger stick" glucose is used instead of SMBG in the figure, which is designed to be easily interpreted by people with diabetes. The different modes of measuring glycemia are closely related, but are not equivalent, and the image is intended as an educational aid. SMBG targets align with the CGM optimal range; however, fasting SMBG levels are recommended to fall between 4 and 8 mmol/L (70–144 mg/dl)

4 | MEASURES OF GLYCEMIA AND TARGETS

4.1 | Glycated Hemoglobin

4.1.1 | Target

A target of <53 mmol/mol (<7.0%) is recommended for all young people with diabetes (Figure 1). Individualized care plans should be a collaboration between the young people with diabetes, their caregivers, and the multidisciplinary team. Where barriers exist to achieving this target (for example access to insulin analogs, advanced technologies like CGM and automated insulin delivery, psychological distress), individualized targets may be selected.

The target of <53 mmol/mol (<7.0%) is chosen with the aim of avoiding long-term microvascular and macrovascular complications.

TABLE 1 Clinical states affecting erythrocyte turnover and their effects on HbA1c

Increased erythrocyte turnover resulting in lower HbA1c	Reduced erythrocyte turnover resulting in higher HbA1c
Recovery from iron, vitamin B12, and folate deficiency	Iron, vitamin B12, and folate deficiency
Pregnancy: second trimester	Pregnancy: third trimester
Chronic kidney disease: Erythropoietin treatment and dialysis	Chronic kidney disease: uremia
Acute blood loss	
Hemolysis (e.g., Sickle cell trait/ disease, thalassemia, G6PD)	
Cystic fibrosis	
Chemotherapy	

The curvilinear relationship of HbA1c and the development of microvascular and macrovascular complications indicates that HbA1c values that approach 42 mmol/mol (6%) may continue to yield risk reduction, but that the relative gains are less as compared with reducing HbA1c levels to the upper limit of the target (53 mmol/mol [7%]).[20,21] An HbA1c target of <48 mmol/mol mmol/mol (6.5%) is recommended during the remission phase or early stage 3 diabetes "honeymoon" and when using contemporary treatment such as continuous glucose monitoring, or automated insulin delivery in combination with a highly skilled specialized workforce adept at diabetes education. This would apply to most young people with diabetes who are not living in a limited resource setting. Other groups recommend this lower HbA1c target of 48 mmol/mol (6.5%) to the diabetes population that they represent (e.g., the 2020 NICE guidelines available at [www.nice.org.uk/guidance/NG18], and Sweden), however, these reflect health care settings where access to the aforementioned technology and workforce are available for the majority of people with diabetes. ISPAD has retained an HbA1c target range between 6% and <7% largely because it represents many populations of people with diabetes around the world who do not have this equity in access.

4.1.2 | Laboratory and practical considerations

Glycated hemoglobin (HbA1c), continues to have a central role in setting glycemic targets, by virtue of several factors; (i) Definitive evidence of the association between HbA1c and the development of diabetes complications,[1,20] (ii) a standardized reference method and procedure set by the IFCC and endorsed by all the major stakeholders,[22] (iii) availability of point-of-care measurement in clinic and in outreach or remote settings, and (iv) barriers to universal access to CGM (and associated glycemic metrics). Every young person with diabetes should have a minimum of four HbA1c measurements per year (at ~3-month intervals). It is recommended that centers regularly audit HbA1c levels, benchmark their data against consensus statements and, if possible, contribute their data to registries and quality improvement initiatives.

The maximum lifespan of erythrocytes is ~100–120 days with an average age at any given time ranging from 40 to 60 days.[23,24] HbA1c reflects average blood glucose concentration in the preceding 8–12 weeks.[25] More recent plasma glucose concentrations contribute proportionately more to the HbA1c concentration—estimated to be 50% contribution from the previous 30 days, with 40% and 10% contributions from the previous 31–90 days and 91–120 days, respectively.[26]

4.1.3 | Limitations of HbA1c

Clinical states associated with altered rates of hemoglobin turnover or erythrocyte survival will affect HbA1c measurements and therefore clinical utility (Table 1). As HbA1c directly reflects average glucose levels, highly variable glucose levels with fluctuating hypo- and hyperglycemia can result in the same HbA1c measurement as an individual with stable glucose levels. This is important as glycemic variability predicts severe hypoglycemia, and there is a growing body of evidence that glycemic variability is an independent risk factor for short - and long-term complications.[27,28] Arguably, CGM, by virtue of providing metrics for both average glucose, glucose out of target range and glycemic variability, as well as having a very high correlation with HbA1c, provides a better reflection of overall glycemia. CGM offers an alternative proxy for HbA1c [the Glucose Management Index (GMI)],[29] however, there is some discordance between GMI and laboratory HbA1c, and hence, the term "estimated" HbA1c should be avoided.[30] Evidence supports the association of diabetes complications and CGM derived measures, particularly time in range.[31] However as widespread CGM uptake has been a more recent phenomenon, it will take time for large registry data to definitively connect CGM metrics with the development of micro- and macrovascular complications. However, where CGM data are not available, evaluation of fructosamine and/or 1,5-anhydroglucitol (1,5-AG) may be the only alternative when HbA1c is not truly reflective of glycemia (Table 1).

Fructosamine is the generic term for plasma protein ketoamines or 1-amino-1-deoxy-D-fructose,[32] and more specifically is the measurement of the total stable irreversible serum glycated proteins at any given time. The half-life of serum proteins is significantly shorter than that of erythrocytes, and the degree of glycation is therefore more reflective of shorter-term alterations in plasma glucose concentrations that is estimated to be 2–3 weeks, which is consistent with the half-life of albumin (20 days) which comprises 80% of total serum proteins.[33,34] 1,5-AG has been proposed in the assessment of glycemic variability.[35] Low 1,5-AG values are indicative of both high circulating plasma glucose concentration, as well as fluctuations in plasma glucose concentrations (hyperglycemic excursions). 1,5-AG concentration reflects plasma glucose concentrations over the preceding 2–14 days.

4.2 | Continuous glucose monitoring

4.2.1 | CGM targets

ISPAD endorses previously published standards for time spent in each glycemic band[36] (Figure 1). These are time spent:

- >70% between 3.9 and 10 mmol/L (70–180 mg/dl),
- <4% <3.9 mmol/L (70 mg/dl),
- <1% <3.0 mmol/L (54 mg/dl),
- <25% >10 mmol/L (180 mg/dl),
- <5% >13.9 mmol/L (250 mg/dl)
- Glycemic variability (%CV) target ≤36%

Average sensor glucose by virtue of a strong correlation between mean sensor glucose and HbA1c, and association with the risk of microvascular complications,[37] and measures of glycemic variability (as a predictor of hypoglycemia), are included. These metrics are all reported as part of standardized CGM reports, termed the ambulatory glucose profile (AGP). When available, CGM targets should be used in conjunction with HbA1c targets (Figure 1). On rare occasions, as discussed above, less stringent time in range goals may be applied where efforts to reach the target may be detrimental to overall wellbeing.

4.2.2 | Practical considerations for continuous glucose monitoring

The evidence and best practice for the use of CGM in improving glycemia and psychosocial burden is reviewed in ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring. This includes appropriate expectation setting and education. Early adoption of CGM from diagnosis is associated with long-term benefits to HbA1c.[38,39] Unfortunately, access to CGM is not universal and can depend on geographic location, local health care funding policy, and socioeconomic status (including insurance). Further, there is racial-ethnic and insurance-mediated bias in recommending CGM by health care providers.[40]

Skin irritation is a significant negative aspect of CGM,[41] and is the commonest reason for discontinuation.[42] Various strategies have been developed to address this issue[43] and are discussed further in ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring and Chapter 19 Other complications and associated conditions in children and adolescents with type 1 diabetes. Alarm fatigue can also contribute to CGM discontinuation, and as such, a person centered approach should be used when introducing CGM alarms.[44]

CGM accuracy is an important consideration, especially in the hypoglycemic range. According to the consensus statement, the maximal allowable time spent <3.9 mmol/L (70 mg /dl) is 4%, however people without diabetes may spend 3.2% of their time in this zone, but rarely <3.0 mmol/L (54 mg/dl), depending on the accuracy of the sensor used.[45,46] Therefore, reducing time spent in the very low <3.0 mmol/L (54 mg/dl) is most important. Fortunately, each subsequent generation of CGM has improved accuracy to the point that several CGM and intermittently scanned CGM (isCGM) systems are approved to be used non-adjunctively. Confirmation of hypoglycemia using a SMBG is recommended. SMBG confirmation should also occur when there is a discrepancy between symptoms of hyperglycemia or hypoglycemia and an apparently normal sensor glucose value.

4.3 | Capillary glucose measurements (SMBG)

4.3.1 | SMBG targets

SMBG targets should be 4–10 mmol (70–180 mg/dl). SMBG levels should be targeted to correspond to an HbA1c <53 mmol/mol (7%). This aligns with the CGM time in range target of >70% between 3.9 and 10 mmol (70–180 mg/dl), and the strong correlation of CGM metrics with HbA1c reviewed earlier. Tighter fasting target range of 4–8 mmol/L (70–144 mg/dl) are recommended in order to achieve the above stated HbA1c target. Previous ISPAD guidelines[16] and current ADA and NICE guidelines have recommended a variety of glucose value ranges depending on time of day and relationship to meals.[16] Without empiric evidence that such specific targeting reduces hyperglycemia or hypoglycemia, combined with the potential for healthcare professionals to send mixed messages and overly detailed education causing confusion, the newly defined SMBG targets offer a pragmatic solution. SMBG glucose level target prior to bed above 3.9 mmol/L (70 mg/dl) are appropriate, however caregivers may have more confidence with higher levels within the 4–10 mmol/L (70–180 mg/dl) range in certain scenarios; for example, if there has been preceding hypoglycemia, peri-exercise, hypoglycemia unawareness, or no access to CGM with hypoglycemia threshold alarms. Ideal glucose levels prior to and during exercise are dependent on many factors including type and duration of exercise, insulin regimen, and CGM use, and are detailed in ISPAD 2022 Consensus Guidelines Chapter 14 for Exercise in Children and Adolescents with Diabetes. The evidence that SMBG has a healthy impact on glycemia in young people with T2D is limited. The potential benefit vs. cost of CGM in this population also remains unclear.

5 | A DEVELOPMENTAL PERSPECTIVE FOR GLYCEMIC TARGET SETTING

While glucose targets outlined above can be applied to all young people with diabetes, a challenging time for the individual and their caregivers can occur as the honeymoon period wanes due to diminishing residual endogenous insulin secretion. Beyond the honeymoon, there may be a requirement for more intensive management and associated burden to maintain glycemic targets. The long-term HbA1c trajectory is strongly predicted early after diagnosis, which highlights the importance of attaining target glucose levels early in the life course.[47–49] As outlined in ISPAD 2022 Clinical Practice Guidelines Chapter 6 on Diabetes Education in Children and Adolescents, it is important that glucose targets be addressed and reinforced during the post honeymoon phase when HbA1c increases and TIR decreases.

The developmental age of the person with diabetes is associated with unique challenges to achieving the aforementioned glucose targets. For example, management in pre-school children can be particularly difficult due to unpredictable eating and activity levels and associated higher glycemic variability.[50] See ISPAD 2022 Consensus Guidelines Chapter 23 on Managing Diabetes In Preschoolers. At school age, young people are beginning independent care. There is

some evidence that focused age-appropriate educational interventions are effective in children and families (See ISPAD 2022 Clinical Practice Guidelines Chapter 6 on Diabetes Education in Children and Adolescents). Further, adolescence is a critical period of independence and physiologic changes associated with increasing insulin resistance, with an increase in HbA1c seen in multiple international registries.[51] Adolescent and culturally appropriate education tools are needed to reinforce individualized care plans that aim to meet glycemic targets while balancing lifestyle and psychological factors (See ISPAD 2022 Consensus Guidelines Chapter 21 Diabetes in Adolescence).

6 | HEALTH CARE PRIORITIES AND FUTURE DIRECTIONS

The social determinants of health, encompassing "the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life (WHO)," strongly predict the likelihood of an individual achieving recommended or optimal glycemic targets.[9,52] ISPAD recognizes that these disparities represent significant barriers to optimal care, and collective efforts are needed to understand and address systemic inequities including medical racism and societal policies that entrench generational poverty. As such, there is a responsibility for health care professionals to advocate on behalf of young people with diabetes who have limited access to healthcare, including technology. Indeed, health providers are known to have implicit bias with respect to offering diabetes technology, which drives inequity.[40,53] Specifically, healthcare reimbursement policies and wider government policy that drives socioeconomic disparities are essential to improve health equity. For the person with diabetes, this should translate to equity in accessing an appropriately resourced multi-disciplinary care team (including dietetic, nursing, psychology, social work, and medical expertise), access to technologies such as CGM and automated insulin delivery, and modern insulin analogs.

AUTHOR CONTRIBUTIONS

All authors reveiwed and summarized literature on glycemic targets. All authors reviewed and edited manuscript drafts. MDB coordinated revisions of the manuscript based on input from ISPAD membership, the co-authors, and ISPAD leadership.

ACKNOWLEDGEMENT

Open access publishing facilitated by University of Otago, as part of the Wiley - University of Otago agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

None of the authors has any conflicts of interest relevant to the subject matter of the article.

DATA AVAILABILITY STATEMENT

This article is an invited review/consensus statement. Data sharing is not applicable.

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How to cite this article: de Bock M, Codner E, Craig ME, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes. *Pediatr Diabetes*. 2022;23(8):1270-1276. doi:10.1111/pedi.13455

DOI: 10.1111/pedi.13442

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Insulin treatment in children and adolescents with diabetes

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KEYWORDS: adolescents, children, insulin, type 1 diabetes

1 | WHAT IS NEW OR DIFFERENT

- Updated insulin treatment sections including new bolus and basal insulin formulations
- Refined recommendations on principles of intensive insulin treatment regimens
- Review of the role and rationale for new insulin analogs, biosimilars and diabetes technology devices for insulin therapy in pediatric diabetology
- Key considerations with regards to access to insulin and affordability

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Insulin treatment must be started as soon as possible after diagnosis (usually within 6 h if ketonuria is present) to prevent metabolic decompensation and diabetic ketoacidosis (DKA). **A**
- Intensive insulin regimens delivered by combinations of multiple daily injections or pump therapy with substitution of basal and prandial insulin aiming to have optimal glycemic level have become the gold standard for the treatment of diabetes in children across all age groups. **E**
- Insulin therapy must be individualized in order to achieve optimal glycemic targets to reduce complications of diabetes. **E**
- Achieving and improving glycemic targets by intensive insulin treatment have been conclusively shown to reduce diabetes complications, comorbidities, and mortality in adolescents and adults. **A** There is no reason to believe this is not the case also in younger children. **E**
- In all age groups, as close to physiological insulin replacement as possible and optimal glycemic control must be the aim using the locally available basal and prandial insulins. **A**
- Insulin treatment must be supported by comprehensive education appropriate for the age, maturity, and individual needs of the child and family regardless of the insulin regimen. **A**

- Aim for appropriate insulin dosage throughout 24 h to cover basal requirements and bolus prandial insulin in an attempt to match the glycemic effect of meals. **E**
- Delivering prandial insulin before each meal is superior to postprandial injection and is preferred if possible. **C**
- Daily insulin dosage varies greatly between individuals and changes over time. It therefore requires regular review and reassessment. **E**
- The distribution of insulin dose across the day shows great individual variation. Regardless of mode of insulin therapy, doses should be adapted to the circadian variation based on the daily pattern of blood glucose levels (BGLs). **B**
- All young people should have rapid-acting or regular insulin available for prevention and management of diabetes hyperglycemia and ketosis emergencies. **E**
- It is essential that a small supply of spare insulin should be readily available to all children and adolescents so that the supply is uninterrupted. **E**
- Children and adolescents should be encouraged to inject consistently within the same area (abdomen, thigh, buttocks, arm) at a particular time of the day, but must avoid injecting repeatedly into the same spot to prevent lipohypertrophy. **B**
- Insulins need to be administered by insulin syringes or other injection devices calibrated to the type and concentration of insulin being used. **E**
- Regular checking of injection sites for site reactions, injection technique and skills to ensure proper insulin delivery remain a responsibility of parents, care providers and health professionals. **E**
- Health care professionals have the responsibility to advise parents, other care providers and young people on adjusting insulin therapy safely and effectively. This training requires regular review, pattern recognition, reassessment and reinforcement. **E**

3 | INTRODUCTION

Insulin has been the core life-saving treatment for diabetes since its discovery in 1921. Near normoglycemia has been well established as a goal of treatment of type 1 diabetes (T1D) based on the results of the landmark *Diabetes Control and Complications Trial* (DCCT). The DCCT and its follow-up study, the *Epidemiology of Diabetes Interventions and Complications* study (EDIC), confirmed that an improvement in long-term glucose control by intensified insulin therapy and extensive support and education, can reduce the incidence of complications and delay the progression of existing complications in T1D, in adolescents and adults.[1]

Despite significant advances in insulin treatment, clinical use of insulin is remarkably complex, and optimal glycemic control can be challenging to achieve and maintain. There is rarely a predictable treatment regimen that always applies to all persons, particularly for children and adolescents with T1D. The insulin requirement of children and adolescents with T1D is never static given the dynamic nature of growth, development, hormonal changes during childhood and adolescence, which necessitates frequent dose adjustments. Consequently, young people with T1D require a customized, highly dynamic, and engaging system to sustain optimal glycemic control and tackle multiple disruptors of daily life.

Exogenous insulin administration that recapitulates as closely as possible the physiologic pattern of insulin secretion by pancreatic β-cells has been considered the ideal insulin treatment to achieve optimal glycemic control. The physiology of insulin secretion includes a basal and a prandial pattern.[2] A healthy pancreatic β-cell secretes continuous basal (low level) insulin and an incremental postprandial (high level) insulin with meals to control BGLs in a tight range.[2] The fundamentals of pediatric insulin treatment attempt to replicate this pattern of basal insulin and prandial insulin secretion. This treatment approach has also been known as basal-bolus insulin or multiple daily insulin injection (MDI). This type of treatment allows more flexibility in the daily lives of persons living with diabetes by partially accommodating variable and sometimes unpredictable eating patterns. Furthermore, in randomized trials, better BG control has been achieved by using MDI regimens, either by insulin injections or pump treatment compared to a twice-daily insulin treatment.[1,3]

Young people with diabetes often require multiple daily injections of insulin, using combinations of rapid-, short-, intermediate-, or long-acting insulin before meals and at bedtime to maintain optimal BG control. Insulin pump treatment is another type of basal-bolus insulin treatment frequently used in children. There is some variation in insulin regimens, both within regions as well as among pediatric diabetologists in the same country, which may be explained by availability, cost or insurance coverage of newer insulin formulations or because of personal preference and experience of the individual with diabetes and their respective diabetes team.

The evolution of insulin formulations over the course of years has broadened the treatment options for the unique needs of young people with diabetes. New insulin analogs and diabetes technology tools have transformed insulin treatment during the past few decades. Regular and NPH/ultralente insulins that were used during the DCCT have been replaced by newer generation insulin formulations in many countries. The rapid-acting and long-acting insulin analogs were developed to provide a more physiologic insulin profile.

The availability of new insulins and the use of new technology have improved the management of diabetes. Increased risk of severe hypoglycemia was an adverse effect of intensive therapy during the DCCT.[1] In contrast to the DCCT experience, recent large diabetes registry studies have clearly shown a diminishing relationship of significant or severe hypoglycemia with lower glycemic targets in people with T1D.[4] On the other hand, the deleterious effect of hyperglycemia on the developing brain has been concerning and highlights the importance of controlling both hyperglycemia and hypoglycemia.[5]

4 | INSULIN FORMULATIONS

Insulin formulations (approved for pediatric use) are listed in Table 1 and are classified in three major groups as prandial, intermediate-acting and basal long-acting insulins. In general, prandial insulins consist of rapid-acting insulins that are intended for bolus injection before meals

TABLE 1 Types of insulin preparations (approved in pediatrics) and action profiles for subcutaneous (s.c.) administration

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Prandial insulins			
Ultra-rapid-acting analog (faster aspart)	0.1–0.2	1–3	3–5
Rapid-acting analogs (aspart, glulisine and lispro[a])	0.15–0.35	1-3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate acting insulin			
NPH[b]	2–4	4–12	12–24[c]
Basal long-acting analog			
Glargine[a]	2–4	8–12	22–24[c]
Detemir	1–2	4–7	20–24[c]
Glargine U300	2–6	Minimal peak	30–36
Degludec	0.5–1.5	Minimal peak	>42

Note: All insulins used must be produced under "Good Manufacturing Practice/Good Laboratory Practice" conditions. Peak and duration of action of a specific insulin formulation is affected by the dose; that is, large doses tend to last longer than small doses.
[a]Biosimilar formulation approved in some countries.
[b]NPH: neutral protamine hagedorn insulin; isophane insulin.
[c]The duration of action may be shorter.

or use in insulin pumps. Basal insulins are long-acting insulins that are intended to be injected not more often than once or twice a day.

4.1 | Prandial insulins

Prandial insulin boluses attempt to mimic endogenous insulin secretion in response to a meal. In response to food intake, the β-cell normally releases insulin in a rapid first-phase followed by a second-phase with prolonged release of insulin into the portal circulation. Rapid-acting insulins (RAI) have been developed to more closely mimic the physiological response of endogenous human insulin to food intake, to improve control of postprandial BG excursions, and to reduce the risk of hypoglycemia.[6] A correction insulin bolus dose of RAI can be given premeal or in-between meals to normalize glycemia.

4.1.1 | Regular (short-acting) insulin

Regular soluble insulin (identical to human insulin) is still used as an essential component in many parts of the world either:

- As pre-meal bolus injections in basal-bolus regimens (given 20–30 min before meals) together with intermediate-acting insulin 2–3 (or even 4) times daily or a basal long-acting analog given once or twice daily.
- Or combined with Intermediate-acting insulin in a twice daily regimen.

4.1.2 | Rapid-acting insulins

RAI is manufactured by modifying human insulin, namely, by changing the amino acid sequence or by the addition of free fatty acid chains to the original molecule that primarily leads to altered absorption from the subcutaneous tissue. These alterations serve one of two main purposes; (1) mimic physiologic prandial insulin secretion by accelerating insulin absorption into the bloodstream for a rapid onset of action relative to human regular insulin and (2) shorter duration of action that provides enough time to control postprandial BGLs while preventing late hypoglycemia.

RAIs have a more rapid onset of action and a shorter duration of activity compared to regular human insulin when administered subcutaneously. This glucose lowering action profile of RAI allows for insulin injection closer to meal onset, allowing postprandial glycemic control with greater flexibility in daily life. In brief, one unit of RAI has the same glucose-lowering effect as one unit of regular insulin, however, the timing profile differs between regular insulin and the RAI.

Three RAIs are approved for use in adult and pediatric persons: insulin lispro (indicated in all persons regardless of age), insulin aspart (≥1 year age), and insulin glulisine (≥6 years age). The three RAIs differ in their amino acid composition and chemical properties, but no significant clinical outcome differences in time of action and duration have been reported.[7–10] They all have a rapid onset and shorter duration of action than regular insulin (Table 1).

We recommend considering the following points when using RAI

- RAI should be given ideally 10–15 min before meals or immediately before meals given the strong evidence that the rapid action not only reduces postprandial hyperglycemia, but nocturnal hypoglycemia may also be reduced.[11–15]
- In exceptional cases, with the goal of matching actual food intake and insulin more closely and minimizing the potential for hypoglycemia in erratic eaters, RAI can be given after the meal to more accurately titrate the insulin doses.[14] Nevertheless, premeal insulin dosing results in lower postprandial BG values for children with more predictable eating habits.[11]

- When hyperglycemia is present, RAI should be given in advance of eating.
- RAIs correct hyperglycemia, with or without ketosis, quicker than soluble insulin owing to their faster glucose-lowering action.
- Are used as prandial or snack boluses in combination with longer acting insulins (see basal bolus regimens).
- Are used in insulin pumps.

4.1.3 | Ultra-rapid-acting insulins

Faster onset and offset of insulin action, replicating physiologic insulin action, is highly desirable to provide greater glycemic control, minimize hypoglycemic episodes and reduce weight gain.

Ultra-rapid-acting insulins are intended to improve the time-action profile of prandial insulins to cover the rapid increase in BG after meals and may be particularly useful for pumps and automated insulin delivery (AID) systems. Because human insulin and RAI generally exist in solution as stable hexamers, the delay in absorption is largely accounted for by the time it takes for hexamers to dissociate into monomers and dimers before they enter the circulation. Faster-acting insulin aspart contains the excipients niacinamide and L-arginine to speed up the monomer formation. This new insulin has a faster onset and offset than aspart insulin and should better control initial post-meal spikes in BGLs and causes less hypoglycemia hours later.[16] The ultra-fast-acting insulin aspart has been approved by the European Medical Agency (EMA) for (children ≥1 year old) and the U.S. Food and Drug Administration (FDA) for (children ≥2 years old).[16]

In children and adolescents with T1D (1–18 years old), mealtime and postmeal faster-aspart combined with insulin degludec provided effective glycemic control compared to insulin aspart in a multicenter, randomized, double blind clinical trial of 26 weeks duration. There were no additional safety concerns for insulin faster-aspart versus insulin aspart throughout the study.

Ultra-rapid-acting lispro is approved for adults with diabetes. The pharmacodynamic and pharmacokinetic action of ultra-rapid-acting lispro has been investigated in a small-scale meal study in children (6–18 years old); however, it is not yet approved for young people with diabetes.

Other investigational ultra-rapid-acting insulin analogs (BioChaperone® Lispro, AT 247)[17] are being tested in adult subjects with diabetes.

Human insulin inhaled powder is the fastest acting exogenous insulin given that the insulin is absorbed quickly from the lungs eliminating the delays after subcutaneous injection. It has been approved in adults with diabetes but is not yet approved for children. A clinical trial of this inhaled insulin for pediatric use is ongoing.

4.2 | Intermediate-acting insulin

For over half a century, isophane NPH (neutral protamine Hagedorn) was the primary form of basal insulin used. The addition of protamine to insulin delayed the dissociation of insulin and slowed the absorption of insulin monomers into the circulation. The duration of action of NPH is longer than that of human regular insulin, but is not sufficient to sustain daily physiological basal insulin needs for people with severe insulin deficiency when given once a day. Its action profile requires twice daily administration to provide the background insulin needed to regulate lipolysis and hepatic glucose production.[18] The strategy is hampered by a small peak that occurs 4–7 h after administration.[19,20]

Insulin regimens based on intermediate-acting NPH and short-acting (regular) insulins have been used for decades to regulate BGLs, however, are limited in their ability to achieve optimal glycemia given the limitations of their insulin action profiles. First, the use of NPH requires a fixed schedule of meals and snacks throughout the day to avoid hypoglycemic events. Second, even more problematic, is the small peak action that occurs with the evening NPH dose. This peak glucose lowering action occurs at the time of minimal insulin need between midnight and 4 am, increasing the risk of nighttime hypoglycemia.[21] In addition, the dose-effect dissipates in the early morning hours (i.e., 4 to 8 am) during the time of greater insulin requirements, contributing to morning hyperglycemia and the so-called "dawn phenomenon"[22] A third problem of NPH insulin is the high day-to-day variability of its glucose lowering action.[19] NPH insulin has to be resuspended by rolling it gently 12 to 15 times prior to injection. Insufficient resuspension of NPH adds to the day-to-day variability of the glucose lowering effect and is reflected by greater glycemic variability and hypoglycemia.[23] The greater variability of the glucose lowering action of NPH insulin compared with newer basal insulins has been verified by various studies.[19,24,25]

Nevertheless, NPH insulin use has some advantages. It costs less than many other basal insulins. The number of daily insulin injections can be reduced because NPH can be mixed with RAI. The peak of NPH action given in the morning may provide some insulin coverage for morning snack or lunch for school-going children who have limited resources to inject insulin at school and have lunch at a consistent time with a consistent amount of carbohydrate everyday[26,27] NPH has been used with regular insulin to prevent hyperglycemia due to intermittent enteral feeds for persons with T1D and T2D.[28,29] In addition, it can be used as a bridge to the longer-acting basal insulins given in the evening when transitioning from IV insulin in the morning or during the honeymoon period.[27,30]

4.3 | Basal insulin analogs

A basal insulin analog is intended to mimic the steady insulin secretion profile of a healthy pancreas during the fasting state. The action of basal insulin secretion is fundamental to stop ketogenesis and hepatic glucose output. Basal insulin coverage may be achieved by subcutaneously injected basal insulin analogs that are grouped as long-acting insulins or continuous subcutaneous infusion of rapid-acting insulin analogs by an insulin pump.

Glargine. Insulin glargine was the first of the newer generation of basal insulin analogs and largely eliminated the need for twice-daily

NPH. Glargine has two modifications made to the human insulin structure including a glycine substitution for asparagine on position A21, and two arginine residues attached to the carboxy-terminal of the beta chain. The resulting shift of the isoelectric point makes glargine soluble at a pH of 4, and precipitates in the neutral pH of subcutaneous fat. This allows for the slow steady release of insulin glargine from its crystalline structure over an approximate 24-h period without a peak. The acidity while in solution has led to complaints from persons in regard to stinging and burning on injecting, yet overall studies appear to show greater quality of life and satisfaction compared to NPH.[31–33]

A multi-national randomized controlled trial (RCT) with 125 children aged 2–6 years using continuous glucose sensors showed once a day glargine was as efficacious as twice daily NPH.[34] While the ideal is to minimize injections and keep glargine to a once daily administration, there are situations that may warrant twice a day regimen.[35,36]

Detemir. Insulin detemir has the amino acid threonine at B30 omitted and a 14-carbon fatty acid covalently attached to the lysine at B29. The fatty acyl side chain stabilizes the hexamers and prolongs the persistence of insulin detemir at the injection site by slowing hexameric dissociation and subsequent monomeric absorption. In addition, the fatty acyl chain enables binding to serum albumin and reduces the amount of free insulin available for engagement with insulin receptors. Subsequently, the disposition of detemir to peripheral tissues and its clearance from the body are slower than regular insulin. Insulin detemir has a slow onset of action, with a peak at 4–7 h and a duration of action up to 20–24 h. The complex then dissociates with a time frame between 6 and 23 h. Anecdotally, detemir insulin causes less local pain compared with the injection of glargine, which is an acidic solution.

Detemir may be administered once or twice daily based on clinical needs and BGL monitoring, but frequently two daily doses are required given its shorter duration compared to glargine. In a pediatric study, 70% of the participants used detemir twice daily.[37] In another trial twice daily detemir showed no clinical advantage over once daily detemir, but those in active puberty often required twice-daily therapy.[38]

When performing conversion between other basal insulins and detemir, prescribers should be aware that higher doses of detemir as compared with glargine may be necessary to achieve the same glycemic control.[39]

Detemir is characterized by a more reproducible pharmacokinetic profile than glargine in children and adolescents with T1D. In comparison to glargine, detemir was shown in a double-blind RCTin children 8 yo to 17 yo with T1D to have less within subject variability.[40] Detemir use has been shown to reduce risk for overall and nocturnal hypoglycemia versus NPH in a 52 week study[24] and a lower risk of nocturnal and severe hypoglycemia compared to glargine in a multicenter study.[41]

In adults, studies with detemir have shown less weight gain, which has been observed also in children and adolescents. Although the precise mechanism remains unclear, it is likely that the weight-sparing effect of insulin detemir can be explained by a combination of mechanisms.[42] Human studies have shown changes in cerebral mechanisms leading to decreased appetite with detemir infusion as well as preferential liver utilization over peripheral tissue resulting in less lipogenesis.[42–47]

Detemir is approved for children by EMA for children ≥1 year old and FDA for children ≥2 years old.

Glargine U300: Glargine U300® is a more concentrated formulation (300 units/ml) of the original insulin glargine U100 product (Lantus®), resulting in flatter pharmacokinetic and pharmacodynamic profiles and prolonged duration of action (>24 h) because of a more gradual and protracted release from the more compact subcutaneous depot. There is less diurnal variation in glucose-lowering activity with U-300 compared with the same dose of U-100 glargine.[48] The full glucose lowering effect may not be apparent for at least 3 to 5 days of use. The EDITION 4 trial, which was a randomized study in adults with T1D, and the EDITION JUNIOR trial, focusing on persons 6–17 years old with T1D, showed non-inferiority of glargine U300 to glargine U100 with similar rates of hypoglycemia and similar glycemic control.[49] However, some studies have shown that glargine U300 has reduced nocturnal hypoglycemia and improved glycemic stability compared to glargine in adults with T1D.[50,51]

U300 is EMA and FDA approved for children ≥6 years.[52]

Degludec. Degludec is a novel ultra-long-acting analog (glucose lowering effect beyond 24 h after subcutaneous injection). The insulin degludec molecule is structured by omitting the B30 threonine from the human insulin molecule and attaching a side chain to the B29 lysine consisting of glutamic acid and a 16-carbon fatty acid with a terminal carboxylic acid group. Degludec forms soluble multihexamers after subcutaneous administration, which then slowly dissociate and results in a slow and stable release of degludec monomers into the circulation. Moreover, the binding of monomers to albumin in the circulation slows the disposition of degludec to peripheral tissues and clearance from the body extending the action for up to 42 h or longer. Because the half-life of degludec is 25 h, dose adjustments are made every 3–4 days without insulin stacking.[53] The pharmacokinetics also allow a lot of flexibility with dose administration and in adults can be given once a day at any time of the day as long as 8 h has elapsed since the previous injection.[54]

Results in young people indicate that the long-acting properties of degludec are preserved also in this age group.[55] More consistent glucose lowering action with degludec is expected once steady state is reached. The long half-life of this basal long-acting analog translates into reduced peak–trough fluctuations and a more consistent glucose lowering action (flatter time–action profile) over a 24-h period. Furthermore, the ultra-long action profile of degludec should allow children to have a less stringent timing of basal insulin administration from day to day, which may be beneficial in the erratic lifestyles encountered frequently in the adolescent population.

In the pediatric regulatory trial, insulin degludec once daily was compared with insulin detemir once or twice daily, with prandial insulin aspart in a treat-to-target, randomized controlled trial (RCT) in children 1–17 year with T1D, for 26 week ($n = 350$), followed by a 26-week extension ($n = 280$). Degludec achieved equivalent long-

term glycemic management, as measured by HbA1c with a significant reduction of fasting plasma glucose at a 30% lower basal insulin dose when compared with detemir. Rates of hypoglycemia did not differ significantly between the two treatment groups; however, hyperglycemia with ketosis was significantly reduced in those treated with degludec, potentially offering a particular benefit for persons prone to DKA.[56] Degludec is EMA and FDA approved for children with diabetes ages 1 year and older.[57]

Once weekly basal analogs. There is ongoing research to develop novel basal insulin analogs intended for once-weekly administration. The Icodec ultra-long acting, weekly basal insulin analog includes three amino acid substitutions (A14Glu, B16His, B25His) that increase molecular stability, reduce enzymatic degradation and insulin receptor-mediated clearance. 20-carbo icosane fatty acid attached to the insulin amino acid chain via a hydrophilic linker to insulin leads to durable binding to circulating albumin and very protracted release. These modifications extend Icodec insulin's half-life to about 8 days with a flat and stable pharmacokinetic profile, low peak-to-trough variations, and evenly distributed glucose lowering efficacy with a weekly dosing interval. There are currently no pediatric data for once weekly insulins.[58,59]

4.4 | Premixed insulin

Premixed insulins contain a fixed ratio mixture of premeal and basal insulins and are not routinely used for diabetes care of children. Premixed insulins eliminate the flexibility offered by separate adjustment of the two types of insulin, which is especially useful for children with variable food intake.

Though not recommended, premixed insulins are infrequently used to reduce the number of injections when adherence to the regimen is a problem. There are limited data regarding the use of premixed insulins in young children. There is some evidence suggesting inferior metabolic control when premixed insulins are used in adolescents. Higher rates of DKA and severe hypoglycemic risk have been reported in children, adolescents, and young adults with TIDM using premixed insulin as compared to a basal-bolus insulin regimen.[60]

Traditionally, premixed insulins were a mixture of NPH and regular insulin (or rapid-acting). The premixed insulins available in various countries have different ratios of NPH/regular (rapid) insulin: 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, 50:50. Premixed insulins are suitable for use in pen injector devices, but require resuspending the insulin before use by tipping or rolling it 20 times to ensure complete and uniform resuspension of NPH insulin.[23]

The most recent addition to the premixed insulin analog group is a mixture of rapid-acting insulin aspart (30%) with long-acting insulin degludec (70%). The insulin degludec and aspart premix showed similar pharmacodynamic properties to the two injections being given separately with the rapid absorption characteristics of aspart and flat and stable profile of degludec maintained separately so the dose can be easily titrated.[61]

Degludec/aspart is approved for children with diabetes by the EMA (children ≥2 year old) and FDA (children ≥1 year old).[62]

4.5 | Safety of insulin analogs

As insulin analogs are molecules with modified structure compared with human insulin, safety concerns have been raised due to changes in mitogenicity in vitro.[63] A potential link between glargine and cancer has been postulated, but in 2013 EMA concluded that insulin glargine–containing medicines (Lantus®, Optisulin®, Sanofi) for diabetes do not show an increased risk of cancer.[64]

4.6 | Biosimilar insulins

Biosimilar insulins demonstrate similarity to existing insulins. In contrast to generic drugs, which are believed to be chemically identical to their reference product, biologics such as insulin demonstrate slight differences in their available counterparts given the use of different manufacturing techniques and materials (e.g., host cells, tissues). The FDA regulatory transition of insulins in March 2020 opened a regulatory pathway for biosimilar insulin products in the United States and led to the approval of three glargine biosimilars (Basaglar: FDA approved for children ≥4 years old; Abasaglar EMA approved for children ≥2 years old; Semglee FDA approved for children ≥6 years old; EMA approved for children ≥2 years old; Rezvoglar FDA approved for children) and a lispro biosimilar insulin for adults and children with diabetes (Admelog FDA and EMA approved for children ≥4 years old 2017, Kixelle insulin aspart approved by EMA 2021 for children ≥1 year old, Sar-Asp EMA approved in 2020 for children ≥1 year old).[65,66]

4.7 | Insulin concentrations

The most widely available insulin concentration is 100 IU/ml (U 100). Regular and NPH insulins are available as 40 IU/ml vials in some countries. The syringe for administering the 40 IU/ml (red cap) insulin is different from 100 U/ml (orange cap). More concentrated formulations (U-200, U-300, U-500) of some types of insulin are available to treat hyperglycemia in severely insulin resistant persons (e.g., individuals requiring more than 200 total units of insulin daily), most commonly in adults.

Very young children, infants, and toddlers occasionally require small insulin doses, therefore may benefit from diluted insulin to allow for more precise dosing and measurement of insulin in <1 unit increments. Insulin is diluted with diluent obtained from the manufacturer. Aspart, Lispro and NPH insulins have special diluents produced by insulin manufacturers. There have been some reports of using normal saline to dilute certain types of insulin when manufacturer diluent is not available. Rapid-acting insulin can be diluted to 1/10 (U10) or U50 with sterile NPH diluent and stored for 1 month[67] for use in pumps

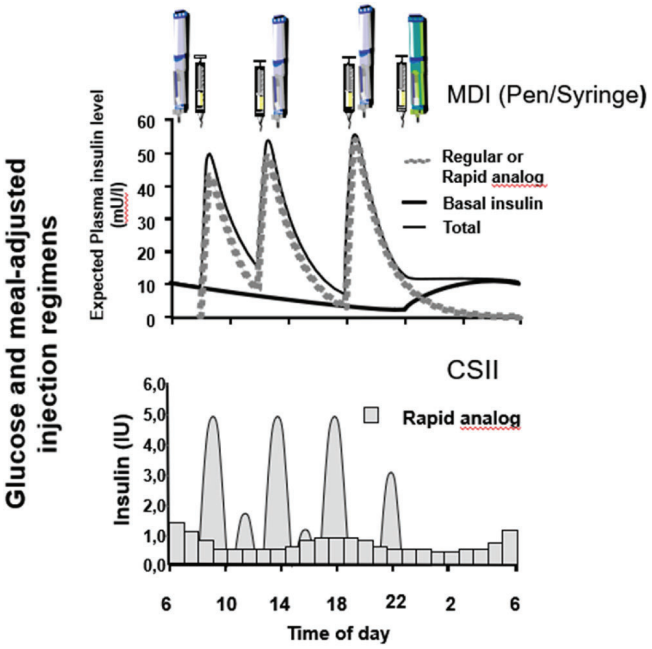

FIGURE 1 Schematic representation of frequently used regimens for insulin therapy in children with diabetes

for infants or very young children. Insulin diluted in a 1/5 ratio (U20 insulin; 20 units/ml) has been used successfully during automated insulin treatment in young children (3–6 years old) with T1D.[68–72] Dosing errors with unconventional insulin concentrations can be serious. Special care is needed in dilution and drawing up the insulin into the syringe. Providers must ensure that persons are well educated about how to use concentrated and diluted insulins safely before it is initiated. Care must be taken to ensure that the same concentration is supplied each time new supplies are received. Parents with children using diluted insulin should inform clinicians regarding the type of insulin they have been using if they transfer their child's care to a new clinic or seek medical care by a clinician who is not familiar with the child's care such as an emergency room clinician to minimize insulin dosing errors.

5 | PRINCIPLES OF INSULIN THERAPY

5.1 | Insulin regimens

The choice of the insulin regimen depends on the availability and affordability of supplies that each health system provides and the personal characteristics of each individual. Since lack of insulin is still considered a major factor influencing therapeutic choices, particularly in children with T1D worldwide, one of the WHO five global coverage targets to be achieved by 2030 is that 100% of people with T1D have access to insulin and glucose monitoring.

Despite clear recommendations for targets of insulin management in children and adolescents with T1D there is considerable variation in the therapeutic regimens and the nomenclature is confusing, but the following classification has been proposed[73] for insulin delivery and is depicted in Figure 1.

I. ***Glucose- and meal-adjusted injection regimens***

- Prandial insulin should be injected before each meal, and ideally giving a dose before snacks as well. Insulin doses are adjusted based on pre-meal glucose level, meal composition (particularly amount and type of carbohydrates) and expected physical activity in the coming hours. Prandial insulin daily requirements are approximately 55% to 70% of total daily dose.
- Basal/long-acting analog is administered once or twice daily; and is approximately 30%–45% of the total daily dose.
- Rapid-acting insulin immediately before[11,12] and adjusted to glycemia, meal content and daily activity. Rapid-acting analogs may need to be given 15–20 min before the meal to have maximum effect, especially at breakfast.[74,75] Ultra-fast-acting analogs may be given closer to the meal.[76–80] If regular insulin is used as prandial insulin, it should be administered 20–30 min before each main meal.[81]

II. ***Pump therapy***

- Insulin pump therapy is extensively reviewed in the chapter "*Technology: Insulin Delivery*" (see ISPAD 2022 consensus guidelines Chapter 17 Technology: Insulin Delivery for details)

III. ***Less intensive and fixed dose regimens***:

- Less intensive regimens include
  - Two or three injections daily using a mixture of short- or rapid- and intermediate-acting insulins.
  - Three injections daily using a mixture of short-or rapid- and intermediate-acting insulins. Beyond the remission or honeymoon period, two injection regimens cannot control BG, and can cause frequent hypoglycemia (particularly in the context of food insecurity) and hyperglycemia
  - Different variations of the timing of administration have been used, but all these therapeutic schemes require a rigid schedule for meals and injections.
  - Prandial insulin is adjusted by glucose levels and carbohydrate content.
- Fixed-dose insulin regimens
  - Fixed insulin dosage either without adjustment or minimally adjusted to daily varying meals. Insulin dosage defines the subsequent mealtimes and their amount of carbohydrates. Due to the limited flexibility, this poses significant challenges for matching it with the day-to-day variability of food intake and activity of children and adolescents.

  Such regimens consisting of two injections daily of a mixture of short- or rapid- and intermediate-acting insulins (before breakfast and dinner/the main evening meal) may be chosen for a short period of time to reduce the number of injections when adherence to the regimen is a problem or during the honeymoon period.

Basal insulin only/premixed insulin only/free mixed insulin combinations are not recommended for the treatment of T1D unless there is no other option.

6 | GUIDELINE ON INSULIN DOSAGE

The appropriate insulin dosage is one that will achieve the best glycemic control for an individual without causing hypoglycemia, hyperglycemia and reducing the likelihood of development of long-term complications. Insulin dosing may be dependent on many factors such as:

- Age
- Weight
- Stage of puberty
- Duration and phase of diabetes
- State of injection sites
- Nutritional intake and distribution
- Exercise patterns
- Daily routine
- Results of BG monitoring and glycated hemoglobin
- Intercurrent illness
- Menstrual cycles

Within a few weeks after the initiation of insulin therapy, it is common for a young person with newly diagnosed diabetes to enter a partial remission phase, also known as the honeymoon period, with an increase in endogenous insulin production. During the partial remission phase, the total daily insulin dose is usually <0.5 IU/kg/day.

Prepubertal children (outside the partial remission phase) usually require 0.7 to 1.0 IU/kg/day and during puberty, insulin dose requirements may rise to between 1 and 2 IU/kg/day.[82] The elevated requirements of insulin during puberty are in part explained by the higher growth hormone secretion that characterizes this period[83] which induces insulin resistance; a phenomenon that is observed during adolescence in persons living with and without diabetes, but is exacerbated in those with diabetes.[84–86]

Higher BGL may be observed during the luteal phase of the menstrual cycle mediated by progesterone.[87,88]

Distribution of Daily Insulin Dose: In children and young people on basal-bolus insulin regimens, the basal insulin may represent between 30% and 50% of total daily insulin and is administered as follows:

- Glargine is often given once a day at approximately the same time each day. However, many children may need to receive two daily doses of glargine or to be combined with NPH to provide full daytime basal insulin coverage.[36,89] Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often with breakfast injection.[19] When switching to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia.[89] Thereafter, the dose should be individually adjusted according to BG trends.
- Detemir is most commonly given twice daily in children.[37,90] When transitioning to detemir from NPH, the same doses can be used to start with, but may require an increase in detemir dose according to SMBG results.[39] A twice daily regimen consisting of NPH injection in the morning and detemir injection at night time with RAI for breakfast and dinner has been used to optimize glycemic control during the honeymoon phase of T1D as a bridge to insulin pump treatment.[27] A broad range of dose adjustments have been described in various small scale studies while switching from glargine insulin to degludec (100%–150% of the glargine dose).[91,92] Minor increase in basal insulin ratio with respect to total daily dose of insulin has been experienced in prepubertal subjects.[92]
- Degludec is administered once daily and can be given at any time. In pediatric persons, degludec is generally given at the same time of the day, but in adults, it can be given at any time of the day as long as 8 h has elapsed since the previous injection. This benefits those with erratic schedules, like adolescents, those who have variable work hours, or individuals traveling across time zones. It is also convenient when transitioning back and forth from insulin infusion pump therapy to injections, as experienced by athletes or adolescents wishing to take a break from the insulin pump. However, given the >24-h duration of action of degludec, care should be taken to reduce the basal pump settings by ~20% for the first 1–2 days when making a switch to the pump to avoid hypoglycemia.
- Glargine U300 is administered once daily at approximately the same time of day. Given its concentrated form of glargine U100 and subsequent longer duration of action, it is particularly helpful for those with high basal insulin needs, or those that desire morning basal insulin administration without the need for an additional evening basal insulin injection.
- NPH insulin has been used in the morning to help cover daytime basal insulin need and glycemic excursions after lunch and snacks in children who are unable to receive insulin injections at school.[26]

Calculation of bolus insulin doses. For intensive insulin treatment, a fundamental aspect is calculating bolus insulin dose based on carbohydrate content and glucose levels.

- The "500-rule" is often used to obtain an initial ratio when starting with carbohydrate counting (divide 500 by the total daily dose—basal and bolus insulin—to find the amount of carbohydrates in grams that 1 unit of bolus insulin [short/rapid/faster-acting insulin] will cover).[93] However, the 500 rule may need to be individually adjusted to allow more insulin for breakfast and less insulin for a meal preceding or immediately after exercise.[94] This "rule" may be different in toddlers and very young children and a 330 or 250 rule (gives 50%–100% more insulin) instead of 500 might be used in preschool-age children. To evaluate and further tailor the child's insulin dosing it is necessary to repeatedly observe and calculate the correct proportion between insulin and CHO from real life

meals. See ISPAD 2022 Consensus Guidelines Chapter 23 on Management of Diabetes in Preschoolers for further details.

- The insulin: carbohydrate ratio (ICR) for an individual meal, for example, breakfast, can be calculated by dividing the carbohydrate content in grams by the insulin dose in units. This method often gives the most accurate results for an individual meal and can preferably be used for breakfast when there usually is an increased insulin resistance. If the BG before and after the meal differ more than 2 to 3 mmol/L (36–54 mg/dl), the correction factor (see below) can be used to calculate out how much more (or less) insulin should be given for a certain meal.
- Fat and protein intake affects the insulin requirements and should be considered for deciding bolus doses. See ISPAD 2022 Consensus Guidelines Chapter 10 on Nutritional Management in Children and Adolescent with Diabetes for further details.
- Correction doses (also called insulin sensitivity factor [ISF], correction factor) can be used according to the "1800 rule," that is, divide 1800 by total daily insulin dose to get the mg/dl that one unit of rapid-acting insulin will lower the BG; for groups that are more insulin resistant, the insulin sensitivity factor has also been calculated dividing 1500 by the total dose. For mmol/L, use the "100 rule," that is, divide 100 by total daily insulin dose.[95] The "1500 rule" maybe used when regular insulin is used for correction dosing.

6.1 | Insulin dose adjustments

Insulin adjustments are essential to reach glycemic goals. The daily or weekly BG patterns and trends measured by self-monitoring of blood glucose (SMBG) or CGM patterns should be taken into account when adjusting insulin doses. The family should be educated and empowered to perform these adjustments.

6.1.1 | Soon after diagnosis

Insulin adjustments should be made frequently to achieve the target BGLs soon after a new diagnosis of T1D. Many centers make daily insulin dose adjustments during the first few week of diagnosis.[96] The appearance of the honeymoon period requires drastic and prompt decreases in insulin daily dose to avoid hypoglycemia.[97,98]

6.1.2 | Insulin dose adjustments for well-established diabetes

Adjustments of insulin dosing are made before meals and adjusted based on glucose levels, obtained either by frequent SMBG or CGM.[89] The long-acting basal insulin dose is titrated to regulate overnight, fasting glucose level. Postprandial hyperglycemia is best controlled by a well-timed injection of prandial insulin and sufficient insulin coverage for the food intake. Correction dose should be added to the prandial insulin dose if premeal BGL is above target range. Post-prandial glucose testing performed at the time of the prandial insulin peak (1.5–2 h after the injection) is essential to determine the glucose lowering effect of prandial insulin dose.

6.2 | Advice for persistent trend deviations from target BGL

- For elevated glucose level before breakfast—the advice is to increase pre-dinner or pre-bed intermediate- or long-acting insulin dose (glucose determination during the night are recommended to ensure that this change does not result in nocturnal hypoglycemia).
- For elevated BGLs after a meal—the advice is to increase pre-meal ultra-rapid/rapid/regular insulin dose.[99]
- For elevated BGLs before lunch/dinner meal—the advice is to increase pre-breakfast basal insulin or increase dose of pre-breakfast ultra-rapid/rapid/regular acting insulin if on a basal-bolus regimen. However, snacking before the meal without an insulin dose should be ruled out. When using rapid-acting insulin in a basal-bolus regimen, the dose or type of basal insulin may need to be adjusted if BGLs rise several hours after the meal (during the post-prandial fasting state) as the analog insulin has most of its effect within 2 to 3 h after injection.[95] Missed mealtime insulin boluses are a major cause of suboptimal glycemia in children and adolescents with diabetes. Omitting >1 meal-related injection per week leads to an increase in HbA1c of 0.3%–0.8%.[100,101] There are new and promising adherence metrics that may be easily interpreted and used for early intervention to improve following the treatment plan during clinic visits.[102]
- Administration of rapid-acting insulin analogs ~15 min before mealtime results in lower postprandial glucose excursions and more time spent in the 3.5–10.0 mmol/L range, without increased risk of hypoglycemia.[75]
- When using carbohydrate counting, persistent elevations of post-meal glucose levels may require adjustment to the insulin to carbohydrate ratio.[103] If post-prandial hyperglycemia persists after correction insulin dosing, the insulin sensitivity factor should be reviewed.
- Unexplained hypoglycemia requires re-evaluation of insulin therapy and dose. Unexplained hyperglycemia may be caused by a "rebound phenomenon," which is described as hypoglycemia followed by hyperglycemia that is potentiated by excessive eating to treat the hypoglycemia along with the effects of hormonal counter-regulation.
- Day-to-day insulin adjustments may be necessary for variations in lifestyle routines, especially exercise or dietary changes.
- Special advice may be helpful when there are changes of routines, travel, school outings, educational holidays/diabetes camps, or other activities which may require adjustment of insulin doses.

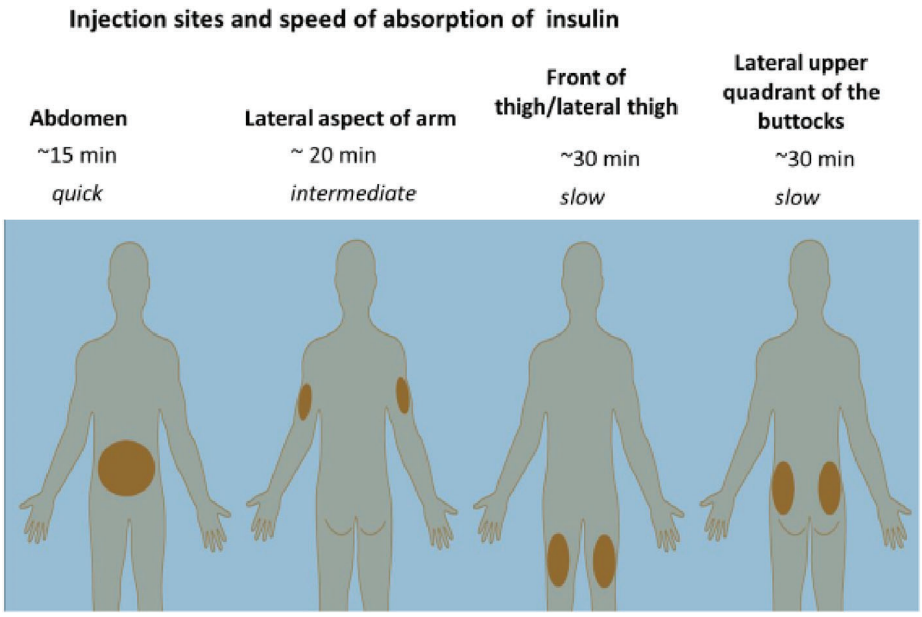

FIGURE 2 Schematic representation of injection sites and relative timing of insulin absorption (Insulin [regular insulin, rapid acting insulin analogs and NPH] is more readily absorbed from the abdomen and deltoid region compared to thigh and buttocks. The long acting insulin preparations has been reported to be less susceptible to changes in absorption rate associated with the site of injection)

7 | ADMINISTRATION AND STORAGE OF INSULIN

7.1 | Insulin injection and absorption

7.1.1 | Injection technique (IT)

Proper insulin injection technique is essential to use insulin safely and optimize glucose control. Insulin should be injected into subcutaneous tissue, not intramuscularly given that intramuscular injection can lead to more rapid and unpredictable insulin absorption and variable effects on glucose. The insulin injection sites are shown in Figure 2, and most important aspects of IT are described in Table 2.

Several other aspects are important when considering the injection technique;

- Needle length. The traditional needle length of 8–13 mm (27 G) were replaced by 4–6 mm needles given that longer needles might increase the risk of intramuscular (IM) injections. The probability of IM injection with the 6 versus 4 mm needle was reported to be dramatically higher in children and adolescents.[104]
- Insulin injections with 4 mm needles has been shown to be the safest strategy for preventing IM injections in children and adolescents.[105]
- Children <6 years old or very thin adults might inject perpendicularly into raised skin. A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection.[106] The pinch-up technique with 4 mm needle is recommended for children ≤6 years old. It should be noted that a "pinch up" method with 5 mm needles may paradoxically facilitate IM injections when children use this technique in the thigh.[107]
- With 4–6 mm needles, the injections can be given perpendicularly without lifting a skin fold but only if there is enough subcutaneous fat, which often is the case in pubertal girls (at least 8 mm as the skin layers often are compressed when injecting perpendicularly).[108] Lean boys, however, have a thinner subcutaneous fat layer, especially on the thigh.[108,109] When injecting into the buttocks, the subcutaneous fat layer is usually thick enough to inject without lifting a skin fold. There is a risk of intradermal injections if 4–6 mm needles are not fully inserted into the skin.
- Rotation of insulin injection sites, within the same injection region, should be taught from diagnosis.
- Pen injection technique requires careful education reinforcing the importance of a 2-unit air shot before every injection to ensure the pen is working correctly.
- The NPH vial should be gently rolled (not shaken) at least 10 and preferably 20 times,[18] to mix the insulin suspension before carefully drawing it up into the clear insulin. The position in which NPH is stored may also affect its activity.[18]
- Injecting cold insulin can sometimes make the injection more painful, therefore, it is recommended that insulin is injected when it is at room temperature.
- A delay of 5–15 s after pushing in the plunger helps to ensure complete expulsion of insulin through the needle.[110]
- Leakage of insulin is common and cannot be totally avoided. Encouraging slower withdrawal of needle from skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site could minimize leakage of insulin.
- Bubbles in insulin should be removed whenever possible. If the bubble is not big enough to alter the dose of insulin it should not cause problems. When using insulin pens, air in the cartridge can

TABLE 2 Most important aspects of the injection technique

1. Have individuals demonstrate their injection technique, either by performing an actual injection or by injecting into a pad or foam pillow. Use this as a teaching occasion, praising what they do correctly and correcting any improper practices.
2. Injections should only be given into clean, healthy sites using clean hands. Disinfecting the skin is generally not required.
3. Injections must be given subcutaneously, not intramuscularly. The 4 mm pen needle has the lowest risk of IM injection and allows wider zones for rotation.
4. Needles that are 12.7 mm in length are not recommended for anyone and persons using 8 mm needles should be switched to shorter ones.
5. The 4 mm needle is preferred for all injectors regardless of age, sex, ethnicity, or BMI. It should be inserted perpendicular to the skin (90° to skin surface)—not at an angle—regardless of whether a skinfold is raised.
6. Very young children (≤6 years of age) and very thin adults (BMI <19 kg/m^2) should always inject with a 4 mm needle into a lifted skinfold. Other children, adolescents, and adults may inject without a skinfold.
7. Inspect injection sites during each visit, at a minimum annually, both visually and by palpation to aid in detection of lipohypertrophy. Make persons aware of the presence of any lipohypertrophy (LH), and instruct them not to inject into it. Use the LH lesion to teach them what to feel and look for and engage them in surveying their injection sites.
8. If lipohypertrophy is found, switch injections to healthy tissue and decrease the dose of insulin. Reductions often exceed 20% of the original dose. Closely monitor SMBG results.
9. Rotate injections systematically to avoid lipohypertrophy, injecting at least 1 cm (approximate width of an adult finger) from previous injections.
10. If possible, avoid reusing needles, which are sterile, one-use devices. Excessive reuse (more than five times) has been associated with lipohypertrophy.

cause drops of insulin appearing on the tip of the pen needle, if withdrawn too quickly.

- Inspection of injection sites and screening for lipohypertrophy regularly is essential to detect insulin injection site scar tissue. Injection sites should be inspected and palpated by diabetes care professionals at every clinic visit and more frequently if lipohypertrophy is detected. Self-inspection of insulin injection sites is recommended in between clinic visits.

Self-injection

There is great individual variation in the appropriate age for children being able to self-inject, depending on developmental maturity rather than chronological age. Most children over the age of 10 years either give their own injections or help with them.[111] Younger children sharing injection responsibility with a parent or other care provider may help to prepare the device or help push the plunger and subsequently under supervision be able to perform the whole task successfully. Self-injection is sometimes triggered by an external event such as overnight stay with a friend, school excursion or diabetes camp. Parents or care providers should not expect that self-injection will automatically continue and be prepared to resume responsibility for the child's insulin injections. Younger children on multiple injection regimens may need help to inject in sites difficult to reach (e.g., buttocks) to avoid lipohypertrophy.

Self-mixing of insulin

When NPH is mixed with short- or fast-acting insulin, it is most important that there is no contamination of one insulin with the other in the vials. To prevent this, the regular (clear insulin) is drawn up into the syringe before NPH (cloudy). Insulins from different manufacturers should be used together with caution as there may be interaction between the buffering agents. Rapid-acting insulin analogs may be mixed in the same syringe with NPH immediately before injecting.[112] It is recommended that neither glargine insulin nor detemir insulin be mixed with any other insulin before injection,[113] because this mixture blunts the early glucose lowering action and prolongs the time-action profile of the rapid-acting insulin as compared with separate injection of the analogs.[113,114]

7.1.2 | Injection site adverse events

Lipohypertrophy is a common complication of insulin therapy. Injection site rotation is necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections.

- Lipoatrophy is rare since the introduction of highly purified insulins; however, recent reports suggest that the frequency of lipohypertrophy continues to be high.[115] Reduction of lipohypertrphy is proven to improve glycemic control. Examination and palpation of insulin injection sites for the presence of lipohypertrophy and other site reactions should be performed during each clinic visit.[116]
- Painful injections are a common concern in children. We recommend checking angle, length of the needle, and depth of injection to ensure injections are not being given intramuscularly and that the needle is sharp if there are concerns regarding painful injections. Reused needles can cause more pain.[117,118] A proportion of people with diabetes have a severe long-lasting dislike of injections which may influence their glycemia. For these persons, an indwelling catheters (Insuflon®, i-port®) or insulin pump therapy can decrease injection pain[118–120] and may improve treatment compliance.[120] These devices may help with frequent injections in the very young child.[118]
- Local hypersensitivity reactions to insulin injections are uncommon but when they do occur, formal identification of the insulin (or more rarely preservative) responsible may be possible with help from the manufacturers. A trial of an alternative insulin preparation may solve the problem. If true allergy is suspected, desensitization can be performed using protocols available from the manufacturers.
- Bruising and bleeding are more common after intramuscular injection or tight squeezing of the skin. Use of thinner needles have been shown to result in significantly less bleeding at the injection site.

7.1.3 | Insulin absorption

Insulin activity profiles show substantial variability both day to day in the same individual and between individuals. Many factors affect speed and consistency of insulin absorption and it is important to be aware of these and to minimize those factors which are modifiable. Young people and their caregivers should be aware of the modifiable factors that can affect insulin absorption.

Factors affecting absorption of insulin[121–123]:

- **Insulin concentration, volume and dose (the subcutaneous depot.)**. Smaller subcutaneous depot,[123] lower insulin concentration[124] and lower insulin doses are associated with faster absorption.
- **Mixture of insulins in the same syringe.** Mixture of certain insulins in the same syringe affects absorption.[113,114]
- **Injection site**. Regular insulin is absorbed fastest from the abdomen, slower from the arm, followed by the thighs and buttocks (Figure 1).[125] These regional differences are less apparent with rapid- and long-acting insulin analogs.[121,122,126,127] The absorption of glargine[128] and degludec are not significantly influenced by the injection site.[129]
- **Intramuscular (IM) injection.** IM administration route is associated more rapid insulin absorption, which is more evident during exercise.[130,131] Accidental IM injection may explain variability in pharmacokinetics between injections in lean individuals and site selection and technique can avoid this.
- **Temperature.** Insulin absorption is increased by local or ambient heating, in both pump and MDI therapy.[132,133]
- **Exercise**. Insulin absorption can be increased with exercise, with the location and depth of the injection being contributing factors.[134] Leg injection with leg exercise leading to faster absorption.[135] Glargine is not affected by exercise.[136,137]
- **Lipohypertrophy**. Lipohypertrophy significantly delays insulin absorption.[138]
- **Obesity**. Increased subcutaneous fat delays insulin absorption due to a reduction in subcutaneous blood flow.[139]

Two devices which apply heat to the injection site have been developed which have been shown to decrease insulin requirements and enhance insulin absorption leading to an earlier peak of insulin action together with less hypoglycaemia. *Insupad* is a device that warms an area 2 cm x 4 cm just prior to injection of bolus insulin and *Insupatch* was developed for insulin pump therapy with an integrated heating element that is activated when a bolus is delivered.[132]

7.2 | Devices for insulin delivery

7.2.1 | Insulin syringes

Syringes are available in a variety of sizes in different countries, ensuring accurate dose delivery, but the following recommendations are desirable.

- Plastic fixed-needle syringes with small dead space are preferable to glass syringes.
- Plastic fixed-needle syringes are designed for single use. Reuse should be discouraged if there is concern about hygiene or injection pain as the needle becomes blunt when reused.[140]
- Small syringes with half- or one unit per mark (e.g., 0.3 ml, 100 U/ml) are preferable for use in small children, making it possible to dose in half units.
- Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U 100 syringes).
- The insulin syringe must match the insulin concentration being used. 40 U/ml syringes (red cap) and 100 U/ml syringes (orange cap) have different markings and cannot be interchanged.
- Syringes must never be shared with another person because of the risk of acquiring blood-borne infection (e.g., hepatitis, HIV).
- It is advisable that all children and adolescents with diabetes should know how to administer insulin by syringe because other injection devices may malfunction.
- Appropriate disposal procedures are mandatory. Specifically designed and labeled "sharps containers" may be available from pharmacies and diabetes centers. Special needle clippers (e.g., Safeclip®) may be available to remove the needle and make it unusable. Without a "sharps container," syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

7.2.2 | Pen injector devices

Pen injector devices containing insulin in prefilled cartridges have been designed to make injections easier, more accurate and flexible. They eliminate the need for drawing up from an insulin vial; the dose is dialed up on a scale and they may be particularly useful for insulin administration away from home, at school or on holidays. When using a pen, it is advisable to count to 10 slowly or 20 quickly (wait about 15 s) before withdrawing the needle from the subcutaneous tissue, in order to give time for any air bubble in the cartridge to expand.[110,140] Pens need to be primed before use, so that a drop of insulin shows at the tip of the needle.

Special pen injection needles of small size (4–6 mm) and diameter are available and may cause less discomfort on injection.[141] Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to half unit increments that are useful for dosing in young children when small dosing increments are needed. A few pens have a memory for taken doses, which can be practical, especially for teenagers. Pen injector devices are useful in children on multiple injection regimens but are less acceptable when insulin mixtures are used. Availability is a problem in some countries since they are a more expensive method of administering insulin.

Insulin pens, vials, cartridges should not be shared.

7.2.3 | Subcutaneous indwelling catheters

Such catheters (e.g., Insuflon®, i-port®) inserted using topical local anesthetic cream, may be useful to overcome problems with injection pain at the onset of diabetes,[118] especially in the very young child. The use of indwelling catheters does not negatively affect metabolic control.[120] In children with injection problems, HbA1c has been lowered by using Insuflon.[119] However, the use of a basal analog and a short- or rapid-acting insulin at the same injection time in an indwelling catheter is not advisable in case of possible interaction of the two insulins.[113,114,119] Indwelling catheters should be replaced every 2–4 days to prevent scarring and a negative effect on insulin absorption.[142,143]

7.2.4 | Automatic injection devices

Automatic injection devices are useful for children who have a fear of needles. Usually, a loaded syringe is placed within the device, locked into place and inserted automatically into the skin by a spring-loaded system. The benefits of these devices are that the needle is hidden from view and the needle is rapidly inserted through the skin. Automatic injection devices for specific insulin injectors are available.[144]

7.2.5 | Jet injectors

High-pressure jet injection of insulin into the s.c. tissue has been designed to avoid the use of needle injection. Jet injectors may have a role in cases of needle phobia. The use of jet injectors has resulted in metabolic control comparable both to conventional injections and continuous subcutaneous insulin infusion (CSII),[145] but problems with jet injectors have included a variable depth of penetration, delayed pain and bruising.[146] In a recent study, using a jet injector for insulin administration was associated with slightly altered variability in pharmacokinetic endpoints, but with about similar variability in pharmacodynamic endpoints compared to conventional administration.[147]

7.2.6 | Continuous subcutaneous insulin infusion

The use of external pumps is increasing and is proving to be acceptable and successful,[145–154] even in young infants.[148,149] For extensive review of CSII please see ISPAD 2022 consensus guidelines Chapter 22 on "Diabetes Technology: insulin delivery."

7.3 | Storage of insulin

7.3.1 | Insulin storage recommendations for insulin not in use

Insulin undergoes chemical and physical degradation over time, leading to reduced potency. This degradation is accelerated by exposure to high temperatures, direct sunlight, shear stress through agitation and increased air-liquid surface, which occurs as the volume of a vial decreases.[155]

Refrigeration problems may be more frequent than apparently thought, household refrigerators often do not meet manufacturers' recommendations, with temperatures often dropping below freezing point.[156] Mail-order insulin, increasingly popular in some countries, might also increase exposure to extended temperature variations. A thermochromic vial monitor technology has been studied to detect if insulin has undergone excessive heat exposure.[157]

Insulin should therefore always be inspected before use and discarded if it has been frozen or if there is any evidence of clumping, frosting, discoloration or precipitation. Individual manufacturer's recommendations for storage and expiration date should be adhered to where possible, and reduced insulin potency considered as a possible cause when insulin requirements increase unexpectedly. For more information on how insulin is stored in the absence of electricity, see ISPAD 2022 Consensus Guidelines Chapter 25 on Managing Diabetes in Limited Resource Settings.

- When not in use, insulin can be stored in a refrigerator at 2–8°C, until the expiration date (not in or too near the freezer section or cooling element).
- Insulin should be discarded if it has been frozen, as freezing can compromise the integrity of both the formulation and the vial itself.

7.3.2 | Insulin storage recommendations for insulin in use

When in use, insulin is regularly exposed to the previously mentioned environmental risk factors and in the case of insulin pumps, which is worn close to the body, not only is the temperature in the reservoir increased, but constant movement can accelerate fibril formation.[158]

- When in use, insulin can be stored at room temperature (below 25 or 30°C) for up to 4 weeks.[145,155,159]
- The time period recommended for use after opening a vial varies between 10 days and 8 weeks for different insulin formulations. We recommend following manufacturer's guidelines and drug inserts. Utilizing smaller volume penfills rather than vials will avoid wastage in children on smaller doses of insulin.
- Insulin used in insulin pumps, should be changed more often. Manufacturers recommend insulin aspart and insulin lispro be kept in the pump reservoir at room temperature for no longer than 6 and 7 days, respectively. Ideally, the insulin in the reservoir should be changed with infusion set/ line changes every 48–72 h. Product information on insulin glulisine states that it can be kept in the pump reservoir for 2 days at 37°C.

Young people and their caregivers should be aware of the importance of optimal storage to maintain potency of their insulin, in particular the avoidance of exposure to high temperatures (e.g., *pumps left in the sun when disconnected, insulin stored in a car glove compartment*).

A number of new insulin delivery devices (pumps, smart pens or pen caps) have an integrated temperature sensor and there are several products available to protect vials and pens from heat. Products dedicated to monitoring insulin temperature using a sensor and mobile app can be kept with any type of insulin and provides a warning when temperature limits are exceeded.

7.3.3 | Storage of insulin when traveling

The following recommendations for transporting insulin during traveling are advised.

- There are several products (bags or cases) on the market for protecting insulin pens and vials from heat, although their performance has not been studied. When using ice packs insulin pens or vials should never be kept directly on ice to avoid freezing. (Hotel refrigerators could be less reliable).
- Insulin should not be in the checked baggage but should always be in the hand luggage carried in the cabin.
- Traveling with extra, back-up insulin is recommended.

8 | INPATIENT INSULIN TREATMENT

Insulin use during inpatient treatment of young people with T1D is required during DKA, peri-operative management and severe infections. Intravenous insulin infusion is preferred in critically ill children. Regular and rapid-acting and ultra-rapid insulins are equally suited for IV therapy.[160] Regular insulin has traditionally been used for IV infusion for inpatient management of diabetes. Non-critically ill children admitted for hospital care could be treated with the currently used subcutaneous insulin regimen with some alterations to the dose.[161]

Therapy with insulin in an inpatient setting might be necessary in certain other scenarios such as hyperglycemia induced by stress perioperatively, parenteral steroids, use of immunosuppressants during chemotherapy (L-asparaginase, tacrolimus, cyclosporine, sirolimus), neurologic drugs used during status epilepticus (valproate, phenytoin), and children with severe burns.[162,163]

8.1 | Intravenous insulin treatment

Treatment with intravenous insulin is the e standard of care in treatment of pediatric DKA[164] and is extensively reviewed in the ISPAD 2022 Consensus Guideline Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State.

8.2 | Subcutaneous insulin

While low-dose insulin infusion is the standard of care for DKA, subcutaneous insulin therapy with aspart or lispro or regular insulin have been used in the management of DKA in adults and children in certain hospitals around the globe.[165–169] The treatment with subcutaneous insulin was important for the treatment during COVID-19 pandemics and was recently reviewed as an ISPAD Guideline Consensus. This suggests use of subcutaneous administration of short-acting (regular) insulin every 4 h as an another alternative treatment method in mild DKA when IV infusion or rapid-acting insulin analogs are not available.[165] A suggested starting dose is 0.13–0.17 units/kg/dose of regular insulin every 4 h (0.8–1 unit/kg/day in divided doses). Doses are increased or decreased by 10–20% based on the BGL before the next insulin injection.[165] Dosing frequency may be increased to every 2 or 3 h if acidosis is not improving.

9 | INSULIN AVAILABILITY AND AFFORDABILITY

Children and adolescents with T1D depend on insulin for survival and should have access to adequate amounts of at least regular and NPH insulin. ISPAD and the international diabetes federation (IDF), through the Life for a Child program, are working toward making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

Although 2021 marked the Centenary of the discovery of insulin, access to this life-saving medicine remains problematic in many settings.[170] The concept of access to insulin needs to be considered with two factors in mind. First, availability: is insulin at the facility or pharmacy when the individual goes to get it.[171] Second, affordability: can the individual pay for their insulin.

Multiple global, national and health system factors impact the prescription of insulin and need to be considered to ensure that barriers do not impact the care provided to individuals by health professionals. Thus, an understanding and discussion of barriers to insulin access should be part of the interaction between healthcare providers and the people they treat. Health professionals should have intimate knowledge of the price of insulin; if insulin is available or not; and what insulin formulations are available in their country in both public and private sectors. This knowledge should help guide persons with diabetes to find the most affordable option to ensure that people with diabetes engage with their insulin regimen as desired.

In parallel, health professionals can also play an active role in ensuring access to insulin by advocating for insulin to be included in the Universal Health Care packages in their countries.

10 | RESEARCH AND NEW DEVELOPMENTS

A century after its discovery, insulin treatment continues to evolve. While insulins with faster onset and shorter duration of action continue to be a hot topic, there has been significant progress in developing ultra-long-acting insulins. Clinical trials investigating the use of weekly insulin formulations have been promising in adult subjects but

not yet tested in children. Another exciting development is *smart insulins*. Smart insulins are glucose responsive insulin formulations that are chemically activated only if the glucose is above the target range; the insulin action ceases once BG is normalized. There are different investigational methods that are used to deliver smart insulins, and smart insulin formulations might be a game changer in diabetes treatment in the future if proven to be safe and efficient.

Combination of insulin with adjunctive medications is another novel intervention to enhance insulin treatment. Long-acting insulin (insulin glargine or degludec) and glucagon-like peptide-1 (GLP-1) receptor agonist premixed injectable products are approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin. Adjunct treatment with premixed insulin has a potential utility to address additional treatment challenges during T1D treatment such as the increasing rates of overweight and obesity in persons with T1D.

Insulins of today continue to save lives of children with diabetes, and insulins of tomorrow will be key to improve the way we treat diabetes and ease the burden of diabetes for people with diabetes.

ACKNOWLEDGMENTS

We would like to thank Dr. Laya Ekhlaspour for her assistance with formatting and references. We would also like to thank the UCSF Pediatric Diabetes Clinic Certified Diabetes Educators and nurses (Monica Mueller, RN, CDE; Mary A. McDonell, MSN, RN, RD, CDE; Betty Katherine-Casto Hynes, MS, RD, CDCES; Nicole Rotter, CPNP) who gave insight and knowledge that considerably aided the revision of the insulin injection section.

CONFLICT OF INTEREST

E. Cengiz is a scientific advisor for Eli Lilly, Novo Nordisk, Adocia and Arecor. TD has received speaker's honoraria and research support from or has consulted for Astra Zeneca, Bayer, Boehringer, Dexcom, Eli Lilly, Lifescan, Medtronic, Novo Nordisk, Provention Bio, Roche, Sanofi, Ypsomed and is a shareholder of Drea Med Ltd. TA, JF, DB, SH, MP, E. Codner have no disclosures.

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How to cite this article: Cengiz E, Danne T, Ahmad T, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Insulin treatment in children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(8):1277-1296. doi:10.1111/pedi.13442

Received: 30 September 2022 | Accepted: 30 September 2022

DOI: 10.1111/pedi.13429

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Nutritional management in children and adolescents with diabetes

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1 | WHAT IS NEW OR DIFFERENT

- The guide to the distribution of macronutrients has been updated and reinforces family preferences and healthy eating patterns
- Food security should be assessed, and advice adapted to the resources of the family
- Consider insulin prescribing and dose adjustment by dieticians where health settings allow
- Continuous glucose monitoring (CGM) is a useful tool for educating both the clinician and young person with diabetes on food related behaviors and the impact of specific meals on glucose levels

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Nutrition therapy is recommended for all young people with diabetes. Nutritional advice needs to be adapted to cultural, ethnic, and family traditions, as well as the cognitive and psychosocial circumstances of the young person and their family. **E**
- Implementation of an individualized meal plan with prandial insulin adjustments improves glycemic outcomes. **A**
- Dietary recommendations are based on healthy eating principles suitable for all young people and families with the aim of improving diabetes outcomes and reducing cardiovascular risk. **E**
- It is recommended that a specialist dietician with experience in pediatric diabetes is part of the multidisciplinary team and available as soon as possible at diagnosis to develop a consistent relationship with the young persons with diabetes and their families. **E**
- Energy intake and essential nutrients should aim to maintain ideal body weight, optimal growth and development and help to prevent acute and chronic complications. Regular monitoring of height, weight, and body mass index (BMI) is required to identify both excessive weight gain and failure to grow normally. **C**
- The optimal macronutrient distribution varies depending on an individualized assessment of the young person. As a *guide*, carbohydrate should approximate 40–50% of energy, fat <35% of energy (saturated fat <10%), and protein 15%–25% of energy. **C**
- Matching of insulin dose to carbohydrate intake on intensive insulin regimens allows greater flexibility in carbohydrate intake and mealtimes, with improvements in glycemia and quality of life. **A**
- Meal-time routines and dietary quality are important to achieve optimal glycemic targets. **B**
- Fixed insulin regimens require consistency in carbohydrate amount and timing for optimal glycemic targets and to reduce the risk of hypoglycemia. **C**

- Pre-prandial insulin dosing should be encouraged from the diabetes onset for young people of all ages. **A**
- Carbohydrate counting is best introduced at onset of type 1 diabetes (T1D) along with education about the impact of mixed meals on postprandial glucose profiles. **E**
- There are several methods of quantifying carbohydrate intake (gram increments, 10–12 g carbohydrate portions and 15 g carbohydrate exchanges). There is no strong evidence to suggest that one method is superior to another. **E**
- The use of the glycemic index provides additional benefit to glycemic management over that observed when total carbohydrate is considered alone. **B**
- Dietary fat and protein affect early and delayed postprandial glycemia. **A** Changes to both the insulin dose and pattern of delivery are needed for meals higher in protein and fat. **A**
- Prevention of overweight and obesity in young people with diabetes is a key management strategy and should be based on a family-oriented approach. **B**
- Repeated episodes of diabetic ketoacidosis (DKA) or worsening glycemic outcomes may be a sign of disordered eating. **C**
- Nutritional advice on how to successfully manage both regular and unanticipated physical activity; and how to meet individual goals in competitive sports is recommended. **E**
- Nutritional management of type 2 diabetes (T2D) requires a family and community approach to address the fundamental problems of excessive weight gain, lack of physical activity and the increased risk of cardiovascular disease (CVD). **E**

3 | INTRODUCTION

Nutritional management is one of the cornerstones of diabetes care and education. Different countries and regions have widely varying cultures and socio-economic statuses that influence and dominate dietary habits. Although there is strong evidence for nutritional requirements in young people, the scientific evidence base for many aspects of diabetes dietary management is still emerging and it is important to individualize nutrition interventions and meal plans.

These consensus guidelines are an update from 2018 that reflect national and international pediatric position/consensus statements[1–4] and, whilst considerations of evidence derived from recommendations for adults with diabetes[5,6] are included, this chapter is aimed at the pediatric and adolescent population. Nutritional advice for young adults (18–24 years) should be based on the adult nutrition recommendations.[5–7]

Dietary recommendations for young people with diabetes are based on population healthy eating recommendations[1,4] and therefore suitable for the whole family. Nutritional advice must be adapted to cultural, ethnic, and family traditions and the psychosocial needs of the individual young person. Regardless of economic status, consideration should be given to food security. Likewise, the choice of insulin regimen, where possible, should account for the dietary habits and lifestyle of the young person.

A pediatric specialist diabetes dietitian should be available wherever possible as part of a pediatric multidisciplinary diabetes care team to provide education, monitoring and support to the young person with diabetes, parents, carers, extended family, nursery, schoolteachers, and babysitters.[8,9] Access to qualified nutrition professionals varies across the world. Recognized qualifications may be in nutrition and/or dietetics. The definition of a dietician according to the international confederation of dieticians is "a person with a qualification in nutrition and dietetics recognized by national authority(s). The dietician applies the science of nutrition to the feeding and education of groups of people and individuals in health and disease." There is currently no information on the number of children living with diabetes who do not have access to a qualified nutrition professional. There are limited data on the impact of access to qualified nutrition professionals in children with diabetes. Data from adult care[10,11] and other long-term conditions[12] support the effectiveness of qualified dieticians and nutrition professionals as part of multidisciplinary care teams.

The dietician should advise on planning, content, and the timing of snacks/meals in the context of each child's individual circumstances, lifestyle, and the insulin action profile of the prescribed regimen. The extended role of the dietician can include adjustment of insulin doses and other medications and, where qualifications are available in countries, prescribing of insulin and other medications. Non-medical prescribing by allied health professionals has been shown to be safe, improve satisfaction, and access to timely advice across a range of long-term conditions.[13,14]

Nutrition therapy, when used in combination with other components of diabetes care, can improve clinical and metabolic outcomes.[15] Nutritional education and lifestyle counseling should be adapted to individual needs and delivered in a person-centered manner. Education can be delivered both to the child/young person and family and in small group settings. It is important that the whole family is involved in making appropriate changes based on healthy eating principles. Regular mealtimes and routines where the child and family sit down and eat together, helps to establish better eating practices and monitoring of food intake and has been shown to be associated with better glycemic outcomes.[16,17]

The impact of diabetes on eating behavior and the potential for psychological disturbances cannot be underestimated. Education should include behavior change approaches, motivational interviewing and/or counseling and should be regularly reviewed to meet the constantly changing needs of the developing child. In order to be most effective, the dietician needs to develop a consistent, trusting and supportive relationship with the families concerned[18,19] and also have clear agreed goals with the multidisciplinary team.[20]

These recommendations target healthy eating principles, glycemic management, the reduction of cardiovascular risk factors, the maintenance of psychosocial well-being, and family dynamics. Use of these recommendations should acknowledge the impact of food security on the ability to follow treatment guidelines.

4 | GUIDELINES ON NUTRITION FOR HEALTH, GROWTH, AND DEVELOPMENT

4.1 | Energy balance

All young people need access to adequate amounts of good quality food that provides sufficient energy to support their growth and development and to maintain a healthy body weight.[21]

When a child or young person is diagnosed with diabetes, a specialist pediatric dietician should assess the food intake and eating patterns of each family and offer advice to help them develop a routine meal plan that meets their child's nutritional needs and provides adequate energy for an active lifestyle.[3,4,8] Young people living with food insecurity (FI), should be offered strategies to alleviate the challenges and stresses experienced which make achieving dietary recommendations for diabetes difficult.[22]

Energy requirements change with growth and regular reviews of their food intake, particularly in younger children, are essential so families can retain flexibility with their meal plans.[4,23] Energy prediction equations are a useful guide to estimate energy requirements in young people, however, these calculations must be individually tailored to an eating plan that is achievable and nutritionally adequate.[24] Regular dietary reviews also help families understand how to adjust total energy intakes with changes in age and stage of development, to promote optimal growth, and avoid restrictive diets[25] or overnutrition that can lead to excess weight gain.[26]

Many young people experience acute weight loss prior to the diagnosis of T1D, followed by an increased appetite soon after initiation of insulin replacement, and this can lead to rapid weight gain if not monitored closely.[27,28] The first year following diabetes onset is a critical period to avoid substantial weight gain and promote maintenance of a healthy body weight over the longer term.[29]

Nutrition education to guide families toward food and drink choices that reflect a balanced energy-appropriate diet will help restore body weight to a healthy range and achieve target glucose levels early on.[3,4]

Total energy intake and appetite can change significantly leading up to (and during) puberty, and this is an important time to routinely reassess individual's nutritional requirements and habitual eating patterns and to consider screening for disordered eating behaviors.[30,31]

4.2 | Maintenance of healthy body weight

Achieving and maintaining a healthy body weight is an important goal in the clinical management of diabetes in young people.[32] The prevalence of overweight and obesity in youth with T1D is at least as high as the general population.[33,34] Global trends in childhood obesity are multifactorial and related to changes in food intake, decreased physical activity, and the obesogenic environment; all contributing to a positive energy imbalance in recent decades.[35] For young people with diabetes other possible causes of obesity include over-insulinization, excess energy intake to avoid or treat hypoglycemia, and additional carbohydrate consumed for exercise.

Diabetes teams can provide family-based guidance on modifiable lifestyle factors such as nutrition, physical activity, and healthy sleep behaviors at diagnosis and on an ongoing basis. At each clinic visit, families can expect that the child/young person will have their height and weight measured, BMI calculated, and growth monitored using appropriate growth charts, to identify any significant changes in weight or failure to grow.[4] Waist circumference and waist/height ratios are less commonly measured in clinic but may be a more useful predictor than BMI of metabolic or cardiovascular risk in some population groups.[34,36]

Dietary review with a specialist pediatric diabetes dietician is recommended for advice to prevent excess weight gain and how to adjust energy intake to support maintenance of a health body weight. Regular review of insulin requirements as children grow can minimize the need for large snacks between meals or before bed to prevent hypoglycemia. Similarly, adjustment of insulin in preference to intake of additional carbohydrate to prevent hypoglycemia during physical activity is recommended.[37]

The use of CGM can be a useful tool to assess amounts of carbohydrate needed to treat hypoglycemia and avoid overtreatment with additional snacks that can contribute to weight gain. The impact automated insulin delivery systems may have on the risk of weight gain in youth with T1D is yet unknown. Healthy food choices in appropriate portion sizes in line with population recommendations are likely to remain a key recommendation.

4.3 | Energy intake recommendations

National guidelines for young people and adults and children with diabetes exist in many countries. Some, including those from Australia and Canada, recommend a carbohydrate intake of at least 45% energy[1,6]; whereas others, such as the UK or US adult recommendations, do not include an amount of carbohydrate expressed as a percentage of energy intake. Clinical consensus is that carbohydrate intakes in older, overweight, or obese adolescents may be lower (40% energy) with higher protein intakes (25% energy).

A guide to the distribution of macronutrients according to total daily energy intake is shown in Box 1.

BOX 1 Macronutrients according to total daily energy intake

- Carbohydrate 40%–50% energy
- Moderate sucrose intake (up to 10% total energy)
- Fat 30%–40% energy
- <10% saturated fat + trans fatty acids
- Protein 15%–25% Energy

BOX 2 Carbohydrate calculation for 7-year-old female with normal activity levels (25th centile weight and height)

DRV	40% Energy as carbohydrate	50% Energy as Carbohydrate	Calculated energy expenditure	40% Energy as carbohydrate	50% Energy as carbohydrate
1703 Kcal/day	170 g/day	212 g/day	1292 kcal/day	129 g/day	161 g/day

These reflect guidelines for healthy eating for young people without diabetes.[38,39] They are also based on food group servings to meet vitamin, mineral, and fiber recommendations for age, without supplementation. An optimal percentage of energy from macronutrients has not been defined and individual and family preferences should be considered.[15] This may vary depending on meal patterns, cultural influences, and metabolic priorities. Restricted access to food may require adjustment of the contribution of carbohydrate to total energy intake to 60% to achieve an adequate intake of other micronutrients and vitamins. Dietary patterns that restrict intake from one macronutrient may compromise growth and lead to nutritional deficiencies.[40]

Translation of the distribution of macronutrients is dependent on the estimation of total energy requirements. Dietary reference values (DRV) are guides for populations[40,41] and individual estimation of energy requirements will ensure appropriate advice is provided. Use of the DRV/daily reference intake (DRI) for energy may result in recommendations to over- or under-consume macronutrients. For example, a calculation for a 7-year-old female with normal activity levels, on the 25th percentile for weight and height versus use of a UK DRV is shown in Box 2.

5 | FOOD COMPONENTS

5.1 | Carbohydrates

Carbohydrate requirements are individually determined based on age, gender, activity, and previous intake. Clinical evidence suggests that individuals can consume 40%–50% energy from carbohydrate and achieve optimal postprandial glycemic targets with appropriately matched insulin to carbohydrate (ICR) ratios and insulin delivery. Healthy sources of carbohydrate foods such as whole grain breads and cereals, legumes (peas, beans, and lentils), fruit, vegetables, and low-fat dairy products (full fat in children under 2 years) should be encouraged to minimize glycemic excursions and improve dietary quality.

5.1.1 | Low carbohydrate diets

There is increasing interest in utilizing low carbohydrate (<26% energy from carbohydrate)[42] and very low carbohydrate (20–50 g/day) diets as an adjunct treatment option for people with T1D.[42,43] Currently, scientific evidence is lacking to support the practice of very low carbohydrate diets or excessive carbohydrate restriction in young people with T1D. Strict adherence to very low carbohydrate diets may result in ketonemia or ketosis, dyslipidemia, and disordered eating behaviors.[40] There is evidence from ketogenic diets that very low carbohydrate diets can be nutritionally inadequate and result in growth failure.[44] Restricted carbohydrate diets may increase the risk of hypoglycemia or potentially impair the effect of glucagon for treatment of severe hypoglycemia.[45]

Whether or not carbohydrate restriction is associated with better health outcomes in young people with T1D is not well-studied. Dietary intake studies in young people using intensive insulin therapy have previously reported an association between lower total carbohydrate intakes and less favorable glycemic outcomes.[46] However, other studies suggest lower daily intake of carbohydrate is associated with lower HbA1c.[47] Current research in the field suffers from the problem of selection and reporting bias as most data come from those families/individuals who choose to follow carbohydrate restricted diets rather than from clinical trials. Clearly, further research is needed to explore potential metabolic and glycemic benefits from moderate carbohydrate restriction in the management of diabetes.

While there is insufficient evidence to recommend very low carbohydrate diets in young people with diabetes, it is important to respectfully explore the reasons families may choose to implement carbohydrate restriction. The perception of what a carbohydrate restriction entails differs among families and diabetes care providers. An emphasis should be on maintaining positive relationships between the family and treating team. If an individual child or family chooses to routinely consume a moderately low (<40% energy) or low (<26% energy) carbohydrate diet they should discuss this with a dietician to ensure the diet is nutritionally complete, particularly in regard to calcium, B vitamins, iron and fiber.[40]

A specialist pediatric dietician will be able to complete a detailed dietary assessment with the family to understand the degree of carbohydrate restriction, discuss the risks associated with restrictive diets in children and adolescents, including eating disorders (ED),[48] and offer a range of strategies the family can use to ensure their goals align with their child's medical needs.[8] Regardless of the amount of carbohydrate in the diet, caregivers and young people with diabetes require strategies to minimize the postprandial excursions caused by carbohydrate. Early prandial insulin administration up to 15–20 min before the meal[49] or the addition of a moderate amount of protein to a meal containing predominantly carbohydrate[50] can assist in reducing postprandial excursions. Substituting low glycemic index (GI) for high GI carbohydrate[51,52] and increasing dietary fiber intake[46] are other useful dietary options.

A meal-time routine with limits on snacking episodes can assist in preventing prolonged periods of postprandial hyperglycemia.[17]

5.1.2 | Sucrose

Sucrose and sucrose-containing food and fluids should be consumed in the context of a healthy diet.[53] Sucrose does not increase glycemia more than isocaloric amounts of starch.[54] However, consumption of foods containing added sucrose should be minimized to avoid displacing nutrient-dense food choices and decreasing dietary quality. If added, sucrose should be appropriately balanced against insulin doses. Sucrose can provide up to 10% of total daily energy intake. Not all countries have a specific recommendation on the percentage of sugar or mono- or disaccharides in the diet.

Sucrose sweetened beverage consumption has been associated with excessive weight gain.[55] Large quantities of sugary beverages cause high postprandial glucose peaks that are difficult to adequately cover with insulin. The consumption of sweetened drinks, soft drinks and cordials should be discouraged for the whole family. Diet or light drinks can be recommended for children with diabetes instead of sugary drinks on special occasions. Sucrose may be used instead of glucose to prevent or treat hypoglycemia.[56,57] See ISPAD 2022 Consensus Guideline Chapter 11 on Management of Hypoglycemia in children and adolescents with diabetes for more details.

5.2 | Fibers

There are wide variations in recommendations and intakes of fiber internationally,[58] and amounts may be expressed as grams/kilocalorie (g/kcal) or grams/day (g/d). Recommendations are often made for adults; children and adolescents are expected to achieve a percentage of the adult recommendations. Reported intakes of fiber are often lower than recommended and vary geographically. Where available, national population guidelines on fiber intake should be followed where no guidance exists the followinFiber recommendations can be used (Box 3).

BOX 3 Fiber recommendations

Age	Fiber recommendations
Birth through 1 year	Not determined
1 year or greater	14 g/4184 kJ (1000 kcals) or 3.3 g/mJ
Alternative formula	
Children >2 years old[59]	Age in years + 5 = gm of fiber per day

Intake of a variety of fiber-containing foods such as legumes, fruit, vegetables, and whole grain cereals should be encouraged. Soluble fiber in vegetables, legumes and fruit may be particularly useful in helping to reduce lipid levels.[60] Processed foods tend to be lower in fiber; therefore, unprocessed, fresh whole foods should be encouraged. Dietary fiber intakes of children in many countries are lower than recommended.[59]

Dietary fiber is associated with digestive health and modulates bowel function, fermentation, and has effects on gut microbiota.[61] Dietary fiber aids in laxation and should be increased slowly to prevent abdominal discomfort and should be accompanied by an increase in fluid intake.[61]

Diet high in whole grains may help to improve satiety, replace more energy dense foods and prevent weight gain.[62] Increasing fiber intake can assist in improving glycemic outcomes,[46] and reducing CVD risk.

5.3 | Fats

Population based nutritional guidelines recommend a fat intake of no greater than 30%–40% total daily energy intake.[25] The American Heart Association supports children consuming a healthy diet which limits saturated fat and recommends replacement with polyunsaturated and monounsaturated fat to reduce CVD risk in later life.[63]

High total fat intakes increase the risk of overweight and obesity[25] and high saturated and trans-fat intakes have been associated with an increased risk of CVD.[1] Studies show that young people with diabetes consume fat and saturated fat above dietary recommendations.[64]

The aim of nutritional advice in clinical practice is to ensure saturated fat, trans fatty acid and total fat intakes do not exceed recommendations for the general population. Monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) can be used as substitutes to improve the lipid profile.[5] Eating patterns that resemble the Mediterranean diet (based on monounsaturated fats, wholegrain carbohydrate, plant-based food choices with a reduced intake of red and processed meats) are likely to be of benefit to long-term health and reduction of CVD risk.[65,66] Care should be taken when giving dietary education that methods of quantifying carbohydrate do not increase total fat and/or saturated fat intake.

- Recommendations for saturated and trans fatty acids should be in line with those for the general population. No more than 10% energy from saturated fat is recommended.[7] Saturated fat is the principal dietary determinant of plasma LDL cholesterol. Saturated fats are found in full fat dairy products, fatty meats, and high fat snacks. Trans fatty acids, formed when vegetable oils are processed and solidified (hydrogenation), are found in margarines, deep-frying fat, cooking fat, and manufactured products such as cookies and cakes. Trans fat should be limited as much as possible.

- Replace saturated fat with unsaturated fats by using lean meats, fish, low fat dairy products and changing to cooking oils and margarines from MUFA and PUFA sources.
- MUFA (particularly cis configuration), found in olive, sesame and rapeseed oils, nuts, and peanut butter may be beneficial in managing lipid levels and confer some protection against CVD. They are recommended replacements for saturated fats.[63]
- PUFA derived from vegetable origins such as corn, sunflower, safflower, and soybean or from oily marine fish may assist in the reduction of lipid levels when substituted for saturated fat.
- Consumption of oily fish rich in n-3 fatty acids is recommended. Advice for children is to eat oily fish once or twice weekly in amounts of 80–120 gm.[67]
- n-3 supplements or an increase in the intake of oily fish should be considered if triglyceride levels are elevated.
- The use of plant sterol and stanol esters (in margarine and dairy products) may be considered for children 5 years and older if total and/or LDL cholesterol remains elevated.[68]

5.4 | Protein

Protein intake decreases during childhood and adolescence from approximately 2 g/kg/day in early infancy to 1 g/kg/day for a 10 years-old and to 0.8–0.9 g/kg/day in later adolescence.[69] Protein promotes growth only when sufficient total energy is available.

Worldwide intake of protein varies greatly depending on economy and availability.

High protein drink and food supplements are generally unnecessary for children with diabetes. Their use requires dietary review with individualized advice.

Sources of vegetable protein such as legumes should be encouraged. Recommended sources of animal protein include fish, lean cuts of meat and low fat dairy products.[1]

When persistent albuminuria, decreased glomerular filtration rate or established nephropathy occurs, excessive protein intake (>25% energy) should be avoided. It is prudent to advise that intake should be at the lower end of the recommended range for age.[70] However, there is insufficient evidence to restrict protein intake. Any modifications to protein intake in adolescence should not interfere with normal growth and requires expert management by a dietician.

5.5 | Vitamins, minerals, and antioxidants

Young people with diabetes have the same vitamin and mineral requirements as other healthy peers.[1] There is no clear evidence of benefit from vitamin or mineral supplementation in children and adolescents with diabetes who do not have underlying deficiencies.[3] Meal planning should optimize food choices to meet recommended dietary allowance/dietary reference intake for all micronutrients. Medical nutrition therapy visits with a dietician are recommended to ensure the child or adolescents' diet is nutritionally complete.

5.6 | Sodium

Young people with diabetes should limit their sodium intake to the recommendations for the general population. Guidelines for sodium intake in children 1–3 years: 1000 mg/day (2.5 g salt/ day); 4–8 years: 1200 mg/day (3 g salt/day); 9 years and older: 1500 mg/day (3.8 g salt/day). High dietary sodium intake in young people with T1D is common and relates to vascular dysfunction.[51]

5.7 | Alcohol and substance use

In young people with T1D, drinking alcohol can contribute to a range of additional health risks, including hypoglycemia and/or hyperglycemia, making them more vulnerable to alcohol-related harms than youth without diabetes.[71] Consequences of alcohol consumption in T1D can include moderate or severe hypoglycemia due to suppression of gluconeogenesis, impaired growth hormone response, alcohol-induced hypoglycemia unawareness, and increased risk of delayed hypoglycemia for 8–12 h after drinking alcohol.[72] Hyperglycemia is another consequence that can be related to drinking and occurs when consuming alcoholic beverages that are high in sugar, or by consuming additional carbohydrate before and after drinking to prevent hypoglycemia.[71,73]

In many countries there are strict limits on the minimum legal age required for the purchase of alcohol, but not always the same level of regulation on alcohol consumption. Alcohol is prohibited in many societies, however where there is exposure to alcohol, studies show adolescents and young adults with T1D have similar or slightly lower rates of participation in drinking alcohol compared to their peers without diabetes.[74,75] For those youth and families who have chosen to include alcohol in their lifestyle, encourage people to ask questions and raise awareness about the negative impact drinking alcohol can have in the short-term on glucose levels and on the long-term on cardiovascular disease (CVD) risk.[76] It is important for pediatric diabetes teams and families to talk with young people about alcohol, and to discuss the facts so that young people are supported to make better choices about drinking. These conversations can be part of a program of education that prepares adolescents for transition to adult services[77] or at any time there is a need identified to reduce the harm of alcohol and substance use.[73,78]

- Young people should be aware of the guidelines for sensible drinking for adults and understand that alcohol consumption is not recommended for children and adolescents.[79]
- Education is needed on the alcohol content of different drinks and what defines a standard drink.
- Carbohydrate should be eaten before and/or during and/or after consuming alcohol. It may be also necessary to decrease the insulin dose, particularly if young people are physically active (e.g., dancing and walking) at the time that they are drinking.
- Young people should be aware there are different types of alcoholic drinks available and understand how these drinks might

impact glucose levels; for example, some drinks contain carbohydrates and can cause initial hyperglycemia, but the alcohol content contributes to risk of delayed hypoglycemia.

- Advice should include avoidance of binge drinking (more than four standard drinks) and young people should be given practical suggestions to reduce alcohol intake if they are exposed over long periods of time, such as having low alcohol drinks or alternating between non-alcoholic sugar-free drinks (including water) and drinks containing alcohol. Low carbohydrate or 'diabetic' beers should be viewed with caution as many do not have reduced alcohol content.
- Alcohol intake in young people may lead to increased risk-taking behaviors and interfere with the ability to recognize hypoglycemia symptoms. It is important to carry diabetes identification and always have quick-acting carbohydrate treatment options available.
- Drinking alcohol can be a risk factor in young people not following their usual diabetes self-care routine, such as checking glucose levels, eating regular meals, adjusting their insulin with physical activity and, as a result, their glucose levels can become unpredictable.[80]
- Excessive amounts of alcohol can cause vomiting and dehydration which can lead to diabetic ketoacidosis (DKA) and hospitalization.[80,81]
- Special care should be taken to prevent nocturnal hypoglycemia by having a carbohydrate snack at bedtime and monitoring glucose levels more often than usual during the night and the following day, at least until lunchtime.[72] CGM can also be very helpful in preventing nocturnal hypoglycemia.
- The health implications of using of cannabis and other substances (including tobacco, vaping and illicit drugs) should be discussed with adolescents and emerging young adults with diabetes as part of their routine care.[78] Cannabis use is associated with changes in appetite and eating behaviors, inconsistent glucose monitoring and insulin administration[73,82] and increased risk of DKA among adults with T1D.[83]

5.8 | Non-nutritive sweeteners and specially labeled foods for people with diabetes

Non-nutritive sweeteners provide insignificant amounts of energy and elicit a sweet sensation without increasing blood glucose or insulin concentrations. FDA-approved sweeteners are safe when consumed within FDA acceptable daily intake amounts (ADI). These are listed in Box 4.

All these FDA approved non-nutritive sweeteners are used in low sugar, "light" or "diet" products to improve sweetness and palatability.

- Country specific guidelines on the intake of sweeteners may exist that should be followed.
- International nutritional guidelines advise that a moderate amount of sucrose can be consumed by people with diabetes[1,5] and foods labeled as suitable for people with diabetes are not necessary. These foods can be more expensive due to the cost of the ingredients, may be high in fat and may contain sweeteners with laxative effects such as polyols (sugar alcohols).
- Polyols (sorbitol, mannitol, erythritol, xylitol, D-tagatose, isomaltose, maltitol, lactitol, and trehalose) are used as sweeteners and bulking agents, are generally recognized as safe by the FDA.[84] Polyols are only partially absorbed from the small intestine, allowing for the claim of reduced energy per gram. Polyols can cause diarrhea at ≥20 gm, especially in children. Some people may be much more sensitive to polyols in smaller amounts.

BOX 4 Acceptable daily intake of non-nutritive sweeteners

Non-nutritive sweetener	Acceptable daily intake (ADI)*
Sucralose	0–15 mg/kg body weight
Saccharin	0–5 mg/kg body weight
Acesulfame K	0–15 mg/kg body weight
Aspartame	0-40 mg/kg body weight
Steviol glycosides (expressed as steviol)	0–4 mg/kg body weight
Monk fruit/Luo Han Guo	Not specified

* https://apps.who.int/food-additives-contaminants-jecfa-database/

6 | FOOD SECURITY

Food security is an important social determinant of health.[85] Food security in a household exists when "all people, at all times, have physical and economic access to sufficient, safe and nutritious food to meet their dietary needs and food preferences for an active and healthy life."[86]

FI is the limitation in the accessibility and/or the lack of resources for nutritionally adequate and safe foods to support normal growth due to household-level economic and social conditions.[87]

In 2019, an estimated 135 million people faced life-threatening FI, according to the World Food Program. Currently, that number has risen to nearly double due to the coronavirus pandemic, with food emergencies afflicting countries that have not required interventions in the past.[88]

Food security should be considered when applying the guidance in this chapter in clinical practice. The impact of FI was seen to be higher in young people and adults with T1D than in those without diabetes.[89] FI increases the risk of less diverse and lower quality diets, reduced micronutrient intake, iron deficiency anemia, and low intake of fruits and vegetables.[90]

The challenges of diabetes management are increased for families facing FI and the associated risks are amplified in children with diabetes, where nutrition plays a vital role in management.[22] Limited budgets lead to purchasing cheaper, energy dense foods, inexpensive poor-quality carbohydrates (refined grains and added sugars), lower nutrient dense foods which may increase dietary glycemic load, and therefore, worsen glycemic outcomes.[91,92] A study conducted in Jordan reported that individuals with diabetes who were severely food-insecure had a significantly higher average BMI, even though they consumed fewer calories than mildly food-insecure or food-secure individuals leading to the "obesity-hunger paradox."[93]

FI can be cyclic and episodic. This pattern of recurrent exposure to inadequate food may result in disordered eating, in particular binge-fast cycles. The cyclic nature of FI may therefore not only result in binge eating behaviors but may also interact with stress pathways that promote obesity.[94,95]

Nutritional counseling for food insecure young people with diabetes should be tailored to fit their incomes and living circumstances. Healthcare providers must try to understand the challenges that may hinder an individual's ability to follow nutrition advice and consider the available resources for purchasing, preparing, and cooking food. Advice to shift dietary intake away from inexpensive carbohydrates and fats and toward vegetables, fruits, protein, and dairy products while acknowledging limited budgets should be given. Discussing portion sizes of food items that are culturally preferable and acceptable to the people with diabetes and their families may be as important as recommending foods that are affordable. Identifying resources within neighborhoods may be a helpful strategy. The kitchen garden concept (growing vegetables in the backyard/terrace) may be appropriate in some settings.[96] Nutrition counseling should include a discussion of how to achieve healthier diets within the means of the family.

7 | GUIDELINES FOR NUTRITIONAL CARE, EDUCATION, AND MEAL PLANNING

Initial dietary advice by a pediatric diabetes dietician should be provided as soon as possible after diagnosis to promote a secure, trusting, and supportive relationship.[2,19] A dietary history should be taken including:

- Pre-existing family dietary habits, traditions, and beliefs
- The child's usual food intake including energy, carbohydrate amount and distribution, fat intake, quality of food choices and mealtimes or patterns of food intake
- The child's daily activities including the impact of nursery/school/work, physical activity, and exercise schedules

Advice should be given at diagnosis based on the dietician's assessment and the individualized plan provided by the diabetes team. Carbohydrate counting is best commenced at diagnosis for those using intensive insulin therapies.[3]

A series of follow-up appointments should be completed with the specialist pediatric dietician within 3–6 months after diagnosis with the first consultation within a month after diagnosis.[97] It is important that the initial assessment includes identification of any body image or weight concerns. Contacts thereafter depend on local arrangements, a minimum should include 2–4 times in the first year and an annual reassessment thereafter.[97] These are necessary to keep pace with the child's growth, modifications to the insulin regimen, lifestyle changes and the identification of specific dietary problems such as dysfunctional eating habits, family issues around food, obesity and EDs. Ongoing support and review by a dietician is essential for optimal care.[3] Frequency of review will be impacted by factors such as changing insulin regimen, mode of insulin delivery, dyslipidemia, need for age-appropriate education, weight gain or weight loss. Co-morbidities such as celiac disease require extra education and dietary intervention with more frequent review.

8 | EDUCATION TOOLS, METHODS, AND INSULIN REGIMENS

Education tools and methods are used to provide knowledge and skills to optimize glycemic management, growth, and CVD outcomes.

- Methods of healthy eating education and tools for carbohydrate quantification are essential.
- Basic dietary education should cover healthy eating with some method of carbohydrate quantification.
- Blood glucose monitoring (pre and postprandial) or CGM provide essential information on postprandial glucose excursions and can direct the education needed, which may be a need to improve carbohydrate counting accuracy, adjustment of prandial insulin timing or amount, or alter the insulin delivery (e.g., a combination bolus) or dose for meals high in fat and protein.[98]
- As families become more confident with managing diabetes, education should be responsive to their observations with whole food education used to explain glycemic index, mixed meal impacts and adjustment of insulin.
- Delivery of education may be face to face, group or virtual. The use of telehealth and virtual consultations may help promote self-care and glucose management and improve access to nutrition education and advice.[99]

8.1 | Healthy eating education tools

Country specific education tools exist for population specific healthy eating education across the world. The Plate Model method (Figure 1) is one example that can be useful in providing basic nutritional information and healthy eating concepts. The plate can be thought of as a

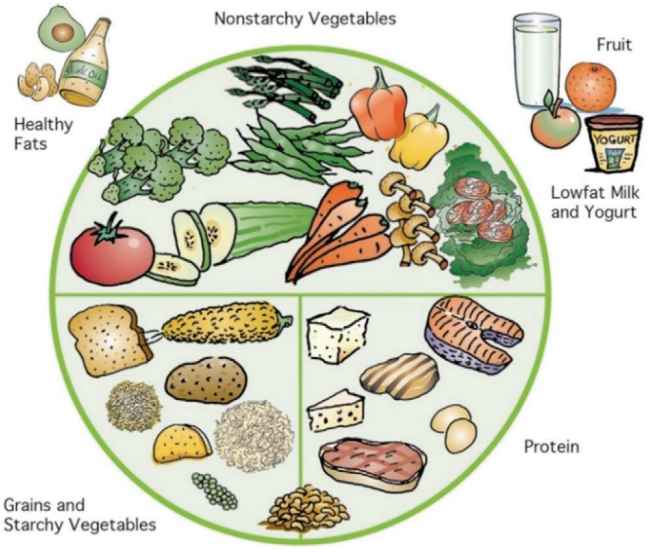

FIGURE 1 Joslin Diabetes Center Healthy Plate Copyright © 2021 by Joslin Diabetes Center (www.joslin.org). All rights reserved. Reprinted with permission

guide to both the individual meal and the whole day. It provides a visual illustration of carbohydrate-containing foods in relation to other food components and is an attractive aid for visual learners. As part of healthy eating education regular meals with small snacks if needed are encouraged to ensure that a range of nutrients are consumed to meet daily recommended requirements.[100]

8.2 | Carbohydrate assessment and methods

The amount of carbohydrate and premeal insulin bolus is one of the most important factors influencing postprandial glycemic levels.[53,101] Other dietary variables such as glycemic index, fat, protein, and fiber impact postprandial glycemia and should be considered when providing education, as well as when interpreting and optimizing postprandial glucose levels.[102,103]

Extensive diabetes education materials are available in many countries to help with the estimation of the carbohydrate content of foods in grams, portions, or exchanges. This approach is usually described as carbohydrate counting. Education sessions involve teaching how to read and interpret food labels, assess the carbohydrate content of the snack/meal, and understand the nutrient content of foods to make healthy choices. Many national diabetes associations also produce useful literature on how to read food labels and count carbohydrate. Education on carbohydrate can improve glycemic outcomes and increase flexibility in food choices.[104] Carbohydrate counting should be part of team-based management approach that includes healthy eating principles and meal-time routines.[23] Information about dietary quality should be provided as part of the education as poor dietary quality has been widely described in young people living with T1D.[105,106]

8.3 | Dietary recommendations for specific insulin regimens

8.3.1 | Twice daily insulin regimens

Twice daily insulin regimens of short- and longer-acting insulin require day-to-day consistency in carbohydrate intake (often as three regular meals with snacks between meals) to match the insulin action profile and prevent hypoglycemia during periods of peak insulin action.[107] Most twice daily insulin regimens require carbohydrate intake before bed to prevent nocturnal hypoglycemia. When other options are available, these insulin regimens should not be used in young people with T1D.

8.3.2 | Intensive insulin regimens

A more flexible approach using individualized insulin to carbohydrate ratios (ICR), which enables the pre-prandial insulin dose to be matched to carbohydrate intake, should be used for children and adolescents on intensive insulin therapy. To assess the accuracy of the ICR, information about postprandial glucose profile is required. Although this method increases flexibility of meal timing and carbohydrate amounts, mealtime routines and dietary quality remain important. International consensus is that carbohydrate counting is best introduced at the onset of diabetes for those using intensive insulin therapy (see ISPAD 2022 consensus guidelines Chapter 9 on Insulin therapy).

Two systematic reviews, based mainly on studies in adults, have reported positive trends in glycemia and lifestyle benefits when carbohydrate counting is used as an intervention for people with T1D.[108,109] These benefits include better HbA1c levels, diabetes-specific quality of life and coping ability in daily life.[109,110]

8.4 | Insulin to carbohydrate ratios

ICRs are used to determine insulin doses based on amounts of carbohydrate. The ICR is individualized for each child according to age, sex, pubertal status, duration of diagnosis, and physical activity. This approach has been endorsed by several international clinical consensus guidelines.[1,3,53] In younger children using CSII, lower percentage basal insulin contribution is effective for achieving high proportion of time in range,[111] and lower total basal insulin will usually result in the use of relatively more bolus insulin for meals, i.e., "stronger" ICRs. A number of formulas using total daily dose for calculation of ICR have been proposed; however, formulas such as the 500 rule initially used in adults can result in "weak" ICRs in children.[112] Younger children often require a "stronger" ICR relative to the total daily dose (i.e., 250 or 330 rules). (See ISPAD 2022 Consensus guidelines Chapter 9 on Insulin therapy). Breakfast may also require a "stronger" ICR than other meals. When assessing ICR the meal composition and the timing of the insulin delivery should also be considered.[113] The postprandial glucose response in the first hour is most likely due to the timing of

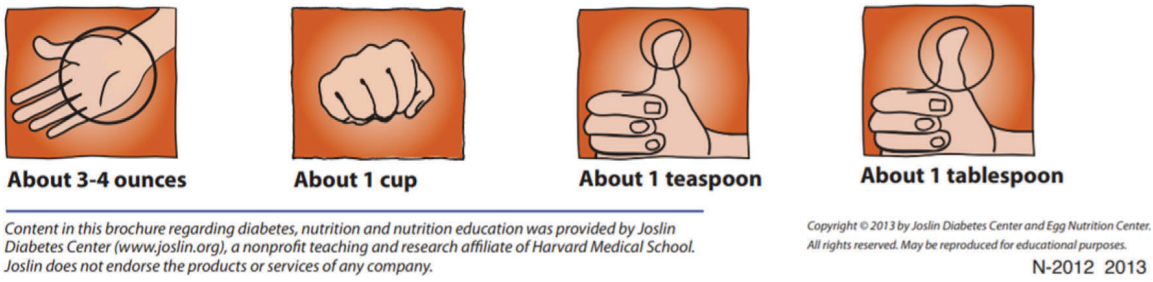

FIGURE 2 Hand measures to estimate amount of food

the insulin, between 90 min and 2 h the predominant factor is probably the amount and GI of the carbohydrate in the meal, and thereafter (late postprandial period), the meal composition.

Studies in adults using multiple daily injections (MDI) with ICRs have shown improvements in dietary freedom, glycemic outcomes, and quality of life,[110] particularly if delivered as part of a comprehensive education package. ICRs have also been evaluated in children and adolescents using MDI, often as part of structured education programs.[114–117]

In a large study of children, adolescents, and young adults, carbohydrate counting was related to better diabetes-specific health related quality of life and optimal glycemic outcomes.[118] A recent small study confirmed improved quality of life associated with advanced carbohydrate counting (ACC) in children.[119]

Research has not demonstrated that one method of teaching carbohydrate counting (grams, portions, or exchanges) is better than any other.[120]

Carbohydrate content of foods can be difficult to assess and there is a need for country and cuisine specific carbohydrate counting resources. ACC requires skills to quantify portion sizes, estimate carbohydrate contents of various foods consumed, read, and understand nutrition labeling on food packages. Access to measuring cups and spoons, food weighing scales, carbohydrate counting resources (pictures, weights, measures of food with carbohydrate counts, nutrition labels, apps, and digital games) are useful tools to learn and estimate the carbohydrate contents of foods.[121,122]

The use of mealtime insulin bolus calculators in both MDI and CSII has been shown to assist insulin dose calculations and potentially improve postprandial glycemia[122–124] and reduce hypoglycemia fear.[125]

Accuracy and consistency in carbohydrate counting are important to optimize postprandial glycemia and reduce glucose variability.[126,127] There is no universal definition for accuracy of carbohydrate counting. Research has shown that children, adolescents and their parents can carbohydrate count with a degree of accuracy, however under and over-estimation of foods remains a challenge.[120] Regular review of carbohydrate counting skills is necessary as children grow and new foods are introduced.[120]

Methods to simplify carbohydrate counting can be used where numeracy and literacy limits the ability of a family to adopt use of grams, portions, and exchanges. The use of the hand size measure is one example. Hand measures (Figure 2) can be used to estimate the amount of food and carbohydrate amount and to teach consistent serving sizes.

9 | GLYCEMIC INDEX AND GLYCEMIC LOAD

The use of the glycemic index (GI) has been shown to provide additional benefit to glycemic management when used in addition to total carbohydrate.[128,129] In T1D, GI should not be used in isolation, but together with a method of carbohydrate quantification.[1] Suggested cut points for classification are high (GI ≥70), medium (GI 56–69), and low (GI ≤55) GI values.

High fiber, low GI foods can help delay the absorption of glucose into the bloodstream, consequently helping to manage blood glucose levels. The GI of a food is influenced by factors such as cooking/preparation method, physical state of a food, type of starch, amount of fat and protein consumed with the food.[130]

A controlled study in children using twice daily insulin, substituting low GI for high GI foods found that a lower GI diet improved glycemic outcomes after 12 months compared to prescriptive dietary advice.[131]

In clinical practice GI is used as a tool to minimize postprandial glucose rises and to improve the quality of the diet.

- Low GI foods may lower postprandial hyperglycemia when they are chosen to replace higher GI foods.[132] This has been demonstrated in a meal study with children using MDI.[51]
- Low GI food sources include whole grain breads, pasta, temperate fruits and dairy products.[133]
- The GI of some foods can differ depending on the geographical location. Dairy products, legumes, pasta, and fruits tend to be low (GIs 55 or less) and are remarkably consistent around the world. Cereals and cereal products, however, including whole grain or whole meal versions, show wide differences, presumably arising from variation in manufacturing methods. Breads, breakfast cereals, rice, and snack products are available in both high- and low-GI versions. Many varieties of potato and rice are high-GI foods, but more low-GI varieties have been identified by research and development.

- Education on GI should incorporate understanding of individual glucose responses to specific foods where information is available from continuous and intermittently scanned glucose monitoring devices.
- The timing and type of insulin delivery may be adjusted depending on the GI of the food. Early delivery of insulin with high GI foods may blunt postprandial glucose spikes and use of a combination type bolus may be beneficial with lower GI foods.[49]

Glycemic load (GL) is another method of predicting the postprandial blood glucose response, which considers both the GI of the food and the carbohydrate portion size.[134] A small pilot study on the feasibility of GL counting in nine adults with T1D found that this method is feasible in real-life for prandial insulin dose calculations.[135] Further studies are needed to investigate the efficacy of GL for calculating the meal-time insulin dose.

10 | MANAGEMENT OF MIXED MEALS

10.1 | Fat and protein

The mealtime insulin dose is typically calculated using an individualized ICR. The impact of fat and protein on postprandial glucose levels has been well established.[103] Observations from pediatric and adult studies have shown that meals high in either protein or fat increase delayed hyperglycemia (up to 3–6 h after the meal) and reduce the early (1–2 h) postprandial rise.[50,136–138] These studies highlight the limitations of carbohydrate-based only formulas for insulin dosage calculations.

Several methods of adjusting insulin doses for fat and protein have been suggested including a formula based on fat protein units (FPU)[139] and the Food Insulin Index (FII) that has been developed and trialed in adults.[140] More practical strategies include making percentage increases in insulin dose based on carbohydrate counting. A higher rate of clinically significant hypoglycemia has been observed in studies using the FPU formula, which is a potential a limitation of this method.[139,141,142] The FII has demonstrated variable outcomes in adult studies.[143,144] A comparison of carbohydrate counting, fat protein units and FII in a pediatric population demonstrated that there was no benefit of FII compared to carbohydrate counting. The FPU formula showed increased postprandial time in range but was associated with an increase in hypoglycemia.[145] Adjusting the original FPU formula may reduce the frequency of hypoglycemia and it has been suggested to consider 200 kcal from protein to require the same amount of insulin as 10 g of carbohydrates.[146]

Management of mixed meals and the impact of fat and protein will depend on the method of insulin delivery and glucose monitoring. Currently most evidence to support optimal insulin bolus dose and delivery for meals high in fat and protein is specific to insulin pump therapy[147]; there are fewer studies to inform management using MDI therapy and hybrid closed loop (HCL) systems.

10.1.1 | CSII

Published systematic reviews of the evidence for insulin dose adjustment for fat and protein provide a range of recommendations, from incremental dose increases up to 30–35% for meals high in fat and protein accompanied by an extended bolus,[49] whereas other reviews suggest increased insulin requirements may range between 25 and 75%, with a starting adjustment of up to 60% dose increase administered 15 minutes before a high protein, high fat meal used with a combination type bolus with the remainder of the dose delivered over 3 hours.[103] However, substantial inter-individual differences exist in insulin dose requirements for fat and protein and individualized advice based on postprandial glucose monitoring up to 6 h is required.[148,149]

10.1.2 | MDI

Data is available from studies showing that additional insulin for high protein and fat meals can be delivered in the pre-prandial injection. Positive outcomes have been reported using a 125% of the calculated insulin dose for carbohydrate content for a high fat and protein breakfast as a pre-prandial injection without adverse outcomes.[150] One study using insulin doses calculated based on carbohydrate, fat and protein content of the meal showed improved postprandial glucose profiles without increased hypoglycemia; in this study the ICR was calculated using a 500-rule based on total daily dose.[151]

- Adjustment of insulin doses for fat and protein should be made when there is evidence of the postprandial impact for the individual. A suggested starting point for additional insulin is a 20% increase in the dose calculated for carbohydrate alone.
- Education on the impact of fat protein is helpful from diagnosis to support understanding of the glycemic impact of mixed meals and foods. Education on assessing postprandial glucose profiles should include understanding of when the raised glucose levels are likely to be due to the timing of insulin delivery (the first 60–90 min), carbohydrate content of the meal/food (90–120 min) fat, protein, and meal composition (120–300+ min).
- Education on the application of evidence of the impact of fat and protein may be beneficial for example, adjusting breakfast content to contain protein to dampen postprandial spike, use of meals higher in protein when delayed hypoglycemia is a risk.

The management of protein and fat in HCL systems is not yet well studied in adults or young people. Clinical experience suggests that individual advice will be needed and some strategies to manage high fat and protein meals may be needed by some people with T1D. To understand the advice that may be needed, the dietician needs to understand how the HCL algorithm adjusts insulin and the bolus options available. The timing of insulin bolus delivery remains important when using an HCL system.[152]

10.2 | Timing and type of insulin boluses

The timing of the prandial bolus is important. Several studies have shown that pre-prandial bolus insulin is preferable to insulin administered during or after the meal.[51,113,153,154] Delivering a bolus dose 15–20 min before eating rather than immediately before improves postprandial glycemia.[113] Newer rapid-acting insulins also require pre-prandial dosing for optimal outcomes. Missed meal boluses negatively impact on glycemic outcomes.[155,156]

One of the advantages of CSII is the ability to tailor prandial insulin delivery to the meal composition. This enables the meal bolus to match the glycemic effect of the meal (low GI, high fat or high protein content).[103]

A systematic review concluded differences in the *duration* and *split* of bolus types across studies, make it difficult to recommend a specific duration and split for *all* meal types.[4949] Studies indicate intra-individual variation in the pattern of insulin delivery required for meals.[103,142] A study in children and adolescents found the optimum combination bolus split to maintain postprandial glycemia with a high-fat and high-protein meal was a 60/40% or 70/30% split delivered over 3 h.[157] However, a study in adults demonstrated the mean optimal pattern of delivery for a high protein, high fat meal was a 30/70% split delivered over 2.4 hours, with a range from 10%/90% to 50%/50% and a delivery duration from 2 to 3 h.[158] Studies have confirmed that the standard bolus is not as effective as the combination bolus for high fat and high protein meals.[157,159] In clinical practice, use of a combination bolus with sufficient insulin upfront to manage the Initial postprandial rise is needed. Initial experience with HCL systems suggests that the timing and delivery of insulin bolus with meals remains central to improved outcomes, with the ICR being one of the settings that the user can adjust.[152]

For those on MDI, it has been suggested from clinical experience at some centers short-acting (regular/soluble) insulin may be given when a prolonged insulin effect is desired. Two studies comparing analog insulin (insulin aspart) and regular insulin have shown no benefit in substituting regular insulin for a faster acting analog.[150,160] Split insulin doses have also been recommended by some centers. One study in adults examining this found that for a high fat, high carbohydrate meal administration of 130% of the prandial insulin dose as a split bolus (100%: 30%), 3 h post meal consumption produced a glycemic response similar to the low-fat (5 g) control condition with no increase in hypoglycemic episodes.[161] When this dose was delivered as a normal bolus however, the incidence of hypoglycemia significantly increased. Pre- and postprandial blood glucose testing at 1, 3, 5, and 7 h or CGM can be useful in guiding insulin adjustments and evaluating the outcomes of changes to the insulin dose or timing.[162]

11 | AGE GROUP SPECIFIC ADVICE

The challenges of nutrition education for young people with diabetes are often age-related and reflect the nutritional and developmental needs of different age groups. Family functioning and interactions at mealtimes have been demonstrated to impact on eating behavior and glycemic outcomes in younger children[163] and adolescents.[164] Below is a summary of the specific characteristics to consider when working with different age groups. See ISPAD 2022 Consensus Guidelines Chapter 23 on Managing Diabetes in Preschool Children and Chapter 21 on Managing Diabetes in Adolescents for more detailed information on the nutritional management in these age groups.

11.1 | Toddler and preschool children

Toddlers have variable appetites. Routine, small meals over the day promote improvements in glycemic outcomes and nutritional adequacy. Grazing on small foods quantities should be discouraged as this may contribute to food refusal at mealtimes and can result in postprandial hyperglycemia. CSII may help manage toddler eating behaviors.[16,165] It is preferable that pre-prandial insulin doses are given,[23] although the dose can be split (a fraction given before and the remainder during the meal) when eating is erratic or new foods are offered.

Positive parental role models and early participation in family meals may promote improved cooperation regarding food and healthy food choices. The re-introduction of a bottle of milk or juice for "easy" carbohydrate intake should be discouraged. Parental anxiety regarding food intake is common in this age group and strategies should be provided for pre-prandial dosing. Daycare providers and babysitters need instruction on diabetes management.

11.1.1 | School-aged children

Diabetes in school

Managing diabetes in a school setting requires a high degree of teamwork, with families, teachers, foodservice providers, non-medical staff, school nurses, and diabetes teams all having an active role to play[166,167] (see ISPAD 2022 Consensus Guidelines Chapter 22 on Management of diabetes in School for more detailed information).

A regular meal and snack plan usually works well in a school environment, although flexibility in the school timetable will be required for children to test glucose levels frequently across the day and be supported to take medications and remedial action to treat hypoglycemia and hyperglycemia as required. Some children will need encouragement to eat their food (and take insulin if required) before going out to play at break times.

Diabetes management plans for each child need to be regularly updated and include information on the child's routine eating plan and management of carbohydrate content of school meals or "lunchbox" food. School staff (including non-medical and school nurses) will require education and support from the family and diabetes team to appropriately supervise children taking insulin before food and apply effective diabetes management strategies.[166,168]

Ongoing education

With supervision and support, the child should start to acquire an age appropriate recognition of carbohydrate foods and understanding of carbohydrate amounts in foods.[120] Advice on healthy food choices, food portion size, and physical activity to reduce the risks of inappropriate weight gain and CVD is important. Although some school-age children are capable of gaining knowledge and skills in carbohydrate counting and glucose monitoring,[120] when arranging playdates, sleepovers and parties, families are encouraged to discuss their child's normal routine for food, physical activity and sleep with other family members and friends, and be available to support their child's diabetes management.

11.2 | Adolescents

Adolescents may choose to be more independent in their food choices and have more freedom on what to eat, when and how much. This can negatively affect their glycemic management and food choices.[169] If adolescents have been diagnosed during their childhood, re-education about the importance of healthy eating, nutrition and diabetes self-management may be needed. Challenging behaviors may include staying out late, sleeping in, skipping insulin, and missing meals and in some cultures, drinking alcohol. Emphasis should be placed on the importance of healthy, routine meals particularly during periods of rapid growth to prevent excessive afternoon or evening snacking. The insulin and meal timing may need to be adapted to suit variable schedules, including school, exercise, and work commitments.

Weight monitoring is recommended for early recognition of either weight loss or inappropriate weight gain. Excessive weight gain requires careful review of insulin dosage, food intake, glycemic management, and physical activity. Weight loss or failure to gain weight may be associated with insulin omission for weight management and may be indicative of a disordered eating behavior(DEB) or an ED. In those with high HbA1c, irrespective of weight profile, further assessment of disordered eating thoughts and behaviors should be considered.

Parties, vacations, peer pressure to eat inappropriately and healthy lifestyle advice all require discussion, problem solving and target setting. Advice on the safe consumption of alcohol and the risk of prolonged hypoglycemia is important in societies where adolescent alcohol consumption is prevalent.

Integrating technology in diabetes care may be attractive to engage adolescents in the decision making of their diabetes and promote healthy behaviors (carbohydrate counting through apps, exercise routines, understanding the impact of different foods in their glucose levels and food diaries).[169]

12 | FESTIVITIES AND SPECIAL EVENTS

Detailed guidance on the management of fasting can be found in the ISPAD 2022 Consensus Guidelines Chapter 24 on Ramadan and other religions fasting.

Special events may include a range of activities including parties, celebrations, and festivities specific to culture and religion. These will all need individual advice and planning according to the insulin regimen.

- Emphasis needs to be placed on the importance of routine with respect to meal timings rather than following an erratic and frequent eating pattern[170]
- Feasting or post fast meals include consumption of high GI foods that also have a high fat, sodium, and calorie content. A nutritional assessment reviewing carbohydrate intake with guidance on making healthy food choices, moderation, portion control, reading nutrition labels, maintaining appropriate energy, adequate hydration and physical activity should be given.
- The principle of carbohydrate, protein and fat counting along with additional insulin and type of bolus (if appropriate) that may be used to manage delayed postprandial blood glucose excursions can be especially useful on these special days. Family involvement and support is crucial in ensuring individual's ability to maintain the diet[96,171,172]
- CGM/frequent self-monitoring of blood glucose (SMBG) can help understand the glucose variability during fasting and feasting. This information can help the health care team in adjusting medications as well as give timely suggestions on meal modification to achieve optimal glycemic outcomes.[173]

13 | NUTRITIONAL MANAGEMENT OF EXERCISE AND PHYSICAL ACTIVITY

Young people with diabetes should be encouraged to participate in regular physical activity because it promotes cardiovascular and mental health and aids weight management. The ISPAD 2022 Consensus Guidelines Chapter 14 on Management of diabetes during exercise provides further detailed explanation of the glycemic impact of physical activity, insulin adjustment strategies and the use of nutrition for hypoglycemia prevention. Adult recommendations on energy balance suggest that participation in general fitness does not necessitate an increase in energy intake above normal recommendations, whereas those who train for >2 h per day will require an increased energy intake.[174,175]

Sports nutrition recommendations for young athletes are adapted from adult recommendations with consideration given to the differences in exercise physiology between young athletes and adults. In T1D further consideration to avoiding hypo- and hyperglycemia is needed. Recommendations that include nutritional intake for adult athletes with T1D are available.[176] Application of these recommendations needs to account for the training or sports regimens, individual glucose responses, and sports aims of the individual athlete.

13.1 | Energy requirements

Energy needs for the young athlete will vary with amount and type of sport being performed. Requirements may be increased above

population guidelines and should be calculated on an individual basis. Requirements may be underestimated by predictive equations.

Low energy availability (LEA) and Relative energy deficiency in sports (RED-s) have been demonstrated to be common in certain populations, including female and adolescent athletes.[177] Whilst no studies have been performed specific to T1D, if LEA is associated to low carbohydrate intake, this will probably increase hypoglycemia risk both during and after exercise. Sports with a requirement for specific body types may pose a higher risk for LEA, for example dance, gymnastics, weight making competitive sports. RED-s has many features of disordered eating and specific screening tools exist (although not validated for T1D), which may be useful in identifying areas of concern.

Adequate total nutrition should ensure that increased energy needs of the sport do not impair growth.[178] The type, intensity and duration, as well as the age, sex, and fitness levels need to be accounted for within an individual management plan. Exercise management plans should emphasize the importance of careful planning, individual attention to detail (blood glucose monitoring, food intake and insulin adjustment) and incorporate the personal experiences of the young person. Advice on overall nutritional intake with a focus on carbohydrate, protein, fluid, and micronutrient intake based in the guidelines presented below should be provided (Box 5).

13.2 | Carbohydrate

The primary fuel for muscles for most types of activity is carbohydrate.[178] Advice on carbohydrate intake for sports performance should be distinguished from advice on carbohydrate intake for hypoglycemia prevention. Based on exercise type, additional carbohydrates may require insulin to enhance utilization and sports performance.[179]

BOX 5 Nutrition guidelines for physical exercise

Protein	1.2–1.8 g/kg/day with 20 g shortly after exercise
Carbohydrate	50% of total energy intake across the day or 3–8 g/kg body weight dependent on exercise intensity 30–60 g per h during exercise lasting longer than 60 min 1–1.5 g/kg body weight within 30 min of finishing of session
Fat	No more than 30% energy intake
Fluid	5–7 ml/kg 4 h before exercise During exercise fluid intake sufficient to minimize body mass changes to <2% After exercise sufficient fluid to replace losses 460–675 ml per 0.5 kg weight loss

To meet the demands of training and recovery carbohydrate intake should be distributed across the day. Specific nutrition advice should cover the pre and post exercise periods.

13.2.1 | Pre exercise period

Prior to exercise (1–3 h), a low-fat, carbohydrate containing meal should be consumed to maximize glycogen stores and availability of carbohydrate for exercise. Assessment of body composition should be considered when using guidelines based on body weight. Young athletes with a greater lean mass may have higher requirements than those of the same body weight or BMI with a high body fat mass. Amounts of carbohydrate required will also be impacted by insulin adjustment, hypoglycemia risk is increased when exercise is performed during peak insulin action. The challenges of sport performed within the school day may make this situation unavoidable. Where possible the guidance in the chapter on exercise management should be followed to adjust insulin based on activity type and glucose trajectory to prevent hypo- and hyperglycemia and support sports nutrition goals. For some high intensity strenuous or anaerobic activities, pre-exercise carbohydrate may also require additional bolus insulin.[180] Food consumed prior to competitive sports may require increased insulin doses compared to training situations. CGM can be used to guide both carbohydrate and insulin adjustments for exercise.[181]

13.2.2 | During exercise

Aerobic exercise lasting 60 min or longer may require additional carbohydrate to maintain performance. Additional carbohydrate needed during activity should be distributed across the activity. Isotonic sports drinks containing 6%–8% carbohydrate may be useful during prolonged activity (>1 h) to address both increased fluid and carbohydrate needs.[182] Examples of suitable carbohydrate sources for exercise include carbohydrate gels, isotonic sports drinks, fruit, and fruit juices. Additional carbohydrate during exercise can cause gastrointestinal upset, so advice should be adapted to suit the individual. Carbohydrate ingestion during exercise should be practiced in training.

13.2.3 | Post-exercise

Carbohydrate intake needs to be sufficient to ensure replacement of both muscle and hepatic glycogen stores, and prevent post-exercise hypoglycemia caused by increased insulin sensitivity during muscle recovery.[180] To aid muscle recovery, it is sensible to consume a low fat, protein and carbohydrate containing meal or snack after training. Carbohydrate mixed with protein may be beneficial in the prevention of post-exercise hypoglycemia.[176,183] Post-exercise carbohydrate needs vary with the intensity and duration of exercise but may be as high as 1.5-g/kg bodyweight.[184] Post exercise carbohydrate will require carefully adjusted insulin doses to reduce glycemic excursions.

13.3 | Protein

Protein is needed for muscle protein synthesis and when consumed with carbohydrate post-exercise may enhance muscle glycogen re-synthesis. The amounts of protein needed to support and enhance sports performance for both resistance and endurance exercise is debated in the literature. For the young people with T1D it is unlikely that total protein intake will be inadequate or that requirements are as high as those stated in adult recommendations. Distribution and timing of protein intake is important and advice about suitable foods to be eaten before and after exercise and before sleep should be given. Adult literature suggests that 25–30 g protein per meal is optimal to enhance muscle protein synthesis.[185,186] Ensuring protein is included in the meal prior to exercise may help reduce the risk of hypoglycemia during exercise.[183] Co-ingestion of carbohydrate and protein post-exercise may help attenuate the risk of late onset hypoglycemia. One study using milk as a post-exercise drink in T1D demonstrated reduced nocturnal hypoglycemia when compared with carbohydrate only drinks.[187] Milk based drinks are recommended as appropriate sources of protein and carbohydrate for enhancing muscle protein synthesis in sports nutrition literature.[188] A further advantage of milk is its leucine content as this has been specifically associated with the ability to train, compete, and recover.[189]

13.4 | Fluid

Fluid intake should be maintained at a level appropriate to the activity to maintain optimal hydration (144). A 1% decrease in body mass has been shown to impair performance.[190] Fluid requirements in young people during strenuous exercise are of the magnitude 13 ml/kg/h. Fluid should be consumed throughout the activity.[191] Water is suitable for most activities up to 60 min duration; however, drinks containing 6–8% carbohydrate are useful when additional carbohydrate is required either for sports performance or hypoglycemia prevention.[192]

13.5 | Micronutrients

Young athletes are at risk of micronutrient deficiency particularly iron (especially females), calcium and vitamin D.[193] Review of food intake should include assessment of intake of these nutrients. Monitoring of vitamin D status is recommended due to increased risk in the young athlete. Correction of vitamin D deficiency may be needed for optimal sports performance.

13.6 | Supplements

Sports nutrition uses a food first approach. Evidence from young sports competitors demonstrates a high use of sports supplements and it is likely that young people with T1D will display similar behaviors. In most cases supplements are unnecessary. Popular supplements used by adolescent athletes include protein supplements and creatine.[194] Young athletes may also be interested in the use of caffeine, which may contribute to hypoglycemia prevention.[195] Counseling on how to use food to maximize training adaptions is essential. Guidance on the use of supplements and the evidence to support their use is available.[196] Advice should include information about the risks of supplement use and guidance on anti-doping according to the sport and level of competition.

14 | NUTRITIONAL MANAGEMENT OF TYPE 2 DIABETES IN YOUNG PEOPLE

The aims of nutritional management for young people with T2D are:

- Achieve normal glycemia and HbA1c[15]
- Prevent further weight gain in those with BMI at 85–95th percentile or achieve weight loss for those with BMI >95th percentile whilst maintaining normal linear growth
- Address co-morbidities, such as hypertension and dyslipidemia

There is little evidence regarding the nutritional management of T2D in young people. Therefore, recommendations are derived from the treatment of overweight and obese children, adults with T2D and young people with T1D. Evidence suggests that there is no ideal macronutrient distribution for weight loss and plans should be individualized.[15] There is some evidence that calorie controlled, lower carbohydrate diets may achieve greater reductions in lipid profiles and diabetes medications; and are therefore an effective strategy for the optimization of T2D management.[197]

Most young people with T2D are overweight or obese, therefore treatment should be centered on education and lifestyle interventions to prevent further weight gain or achieve weight loss while maintaining normal linear growth. The entire family should be included in the lifestyle intervention since parents and family members influence the child's food intake and physical activity and they are often overweight or obese and also have diabetes.[198] Families should be counseled to decrease energy intake by focusing on healthy eating, strategies to decrease portion sizes of foods, and lowering the intake of high energy, fat and sugar containing foods. Simply eliminating sugary beverages such as soft drinks and fruit juices can accomplish improvement in blood glucose and weight.

Increasing energy expenditure by increasing daily physical activity to 60 min daily is an important component of treatment.[199] Limiting sedentary behaviors, such as television viewing, video games, and computer use has been shown to be an effective way to increase daily physical activity and help maintain or achieve a healthy weight in children. Physical activity may also help lower lipids in adolescents with diabetes.[200]

Medical nutrition therapy should be provided to prevent and treat co-morbidities including obesity, dyslipidemia, hypertension, and micro- and macro-vascular complications.[2]

Very low-calorie ketogenic (VLCK) diets can be safely and effectively used in the management of young adults with T2D.[201] Clinical experience suggests obese older adolescents with T2D may also benefit from a carefully monitored VLCK weight loss program.[202]

15 | MANAGEMENT OF CO-MORBIDITIES

15.1 | Dyslipidemia

Dyslipidemia is often overlooked or inadequately treated in young people with diabetes, even though CVD remains a major cause of mortality in adults with diabetes.[203] Hyperglycemia, insulin deficiency and insulin resistance are associated with dyslipidemia, thus the initial therapy should be to optimize glucose management. The management of dyslipidemia requires a comprehensive approach, which includes attention to medical nutrition therapy (Box 6).[2,204]

If dyslipidemia persists despite these measures or in the face of multiple risk factors for CVD, pharmacological treatment should be considered according to published guidelines.[204]

(For further guidance on pharmacological treatment, please refer to chapter 18 Microvascular and macrovascular complications in children and adolescents and Chapter 3 Type 2 diabetes in children and adolescents)

15.2 | Celiac disease

Celiac disease (CD) is more common in children with T1D than in the general population.[205] (see Chapter 19 Other complication and associated conditions in children and adolescent).

A gluten-free diet (GFD) is the only available treatment for CD. The GFD requires elimination of wheat, rye, barley, triticale, possibly oats and products derived from these grains, brewer's yeast, malt, and food products with artificially added gluten or cross-contaminated with gluten.[206] Alternatives such as rice, preferably brown/unpolished rice, and millets, quinoa, legumes/pulses, buckwheat, amaranth, potato, corn, soy, tapioca, maize, water chestnut, and products derived from these must be used as substitutes.[207]

Recommendations to exclude oats vary between countries. Short- and long-term studies involving children and adults suggest that oats can be safely included for most people; however, a small minority of people with CD have been found to react to oats.[208] Research supports the view that gluten-free oats (oats not contaminated with gluten) may be acceptable in moderate amounts (20–25 g/day dry rolled oats for children: 50–70 g/day for adults) for the majority but not all children with celiac disease.[207–209]

The definitions of a GFD vary across the world; in Europe, Canada and USA foods containing less than 20 parts per million (ppm) (20 mg/kg) gluten are considered suitable for a GFD (even if gluten is detectable) in accordance with Codex Alimentarius.[210] Wheat starch is used in some European countries as part of a GFD, whereas it is not recommended for inclusion in Australia and New Zealand, where the legal definition states that foods must not contain any detectable gluten (less than three parts per million) if labeled as gluten-free.[211] There are no published studies to determine if there are differences in short- and long-term outcomes with the more stringent levels of gluten restriction.

GFD has been shown to result in more glycemic excursions in both adults without T1D or CD,[212] and in those with T1D and CD.[213] In a study of adults with T1D and CD, the use of fiber enriched buckwheat pasta produced less glycemic variability than corn pasta.[214] Strategies such as lower GI, higher fiber food choices, and ensuring early pre-prandial insulin administration may assist with reducing glycemic variability.

Emphasis should be placed on the nutritional quality of the GFD, particularly iron, folate, magnesium, zinc, calcium, iodine, fiber, and B vitamin intakes.[215] Nutritional deficiencies arising from a GFD can be avoided by including naturally occurring local GF whole grains, fruits, vegetables, plant and animal sources of protein, dairy, fats and oils, gluten-free commercial products that have been fortified or enriched and avoiding processed, high fat and sugar packaged foods. This will help lower the GI of the meals which are significantly altered when on a GFD.[215]

Probiotics may improve gastrointestinal symptoms in individuals with CD,[216] although more evidence is required to prove the efficacy of their therapeutic use and clinical impact in CD.

It is common for people with diabetes who develop CD to have challenges with maintaining GFD. A better understanding of the diet as well as access to a dietician and regular follow up may improve nutrition management.[217] Dietician-led follow-up visits have shown to provide lower long-term costs.[218] Factors reported to assist with GFD maintenance include adopting the GFD within the first year of diagnosis, younger age, and having family meals.[219] Young people with maladaptive eating behaviors, which are similar to risk factors for EDs, will require ongoing follow-up with gastroenterologists and dietitians plus psychosocial support to improve quality of life.[220]

BOX 6 Medical nutrition therapy for dyslipidemia in diabetes

- Reduce saturated fat intake to less than 7% and eliminate trans fats.
- Total dietary fat: 25%–35% of energy
- Diet rich in fruits and vegetables (>5 servings a day)
- Increase dietary sources of both soluble fiber and antioxidants
- Eliminate sugar-sweetened beverages and juices
- Reduce highly processed food products
- Savpid smoking

Providing educational materials (list of gluten-free foods, nutrition label reading, recipes, eating out and travel guidelines) and access to support groups, social workers, or family counseling will help improve healthy eating and maintaining GFD.[215]

15.3 | Disordered eating behavior and eating disorders

ED and DEB are more common in young people with diabetes than their peers.[221] DEB is a term used to describe a variety of disturbed eating behaviors whereas an ED is a clinical diagnosis. DEB include intentional over- and underdosing of insulin, dietary restriction, and self-induced vomiting.[31,222] Diabetes is unique in making it possible to manage weight and body shape without overt avoidance of food by means of insulin restriction. Insulin omission for reducing weight has been reported in pre-teens, adolescents and young adults and is more common in girls and young women.[223]

Diabulimia is a term that casually refers to the purging of calories through insulin restriction with the aim to lose weight or alter body shape. Diabulimia is not a clinical diagnosis and lacks a clear definition, which may lead to inaccurate descriptions of DEB and subsequently inadequate treatment. More work is needed to determine the optimal treatment strategy of young people with either diagnosed eating disorders or poorly defined disorders (see ISPAD 2022 Consensus Guidelines Chapter 15 on Psychological care of children and adolescents with T1D).

Detecting eating problems can be difficult as attention to diet and benefits of avoiding certain foods is fundamental parts of usual diabetes care. A range of screening questionnaires and structured clinical interviews are available to help identify ED and DEB in children and young people with T1D.[224,225] The Diabetes Eating Problem Survey-Revised (DEPS-R) is a 16-item diabetes-specific self-report screening tool for disordered eating that can be completed in <10 min during a routine clinical appointment.[224] The DEPS-R has been validated in several languages and can be used as a screening tool at clinic visits.[224,226,227] A recent study from Australia showed insignificant utilization of screening tools in pediatric clinics and low reported rates of ED, emphasizing the importance of both using existing tools as well as the need for user-friendly screening tools.[228] The majority of questionnaires are in English, creation of screening tools in more languages is required for non-English speaking countries. One article has found a single screening question; "Have you ever been overweight?" to have high precision in at risk individuals for further screening and early interventions.[229] Acknowledging risk factors and being attentive to signs and symptoms of DEBs can prevent progression to clinical eating disorders and further deterioration of glycemic management. See Box 7.[31]

The risk for ED increases with diabetes duration and age.[230] This is of clinical importance as adolescents transition into adulthood and require continuity of care, often across two diabetes teams. Extra attention should be paid to girls as they are more prone to DEB and are more likely to meet criteria for overweight/obesity as well as have less favorable metabolic outcomes, all risk factors for ED.[31,223,229]

BOX 7 Risk factors and indicators of disordered eating behaviors in people with diabetes

Risk factors	Warning signs suspicion for early detection	Confirmation screening tools
• 7–18 years • Female • Detailed meal planning, precision in food proportion • Overweight, obesity • Body dissatisfaction • Anxious, poor quality of life • Poor attention in family to healthy eating, maternal overweight or binge-eating disorders in mothers	• Suboptimal glycemic management • Recurrence of hypoglycemic events • Systematic calculations of caloric values and weighing of foods • Frequently missed medical check-ups • Refusal to be weighed • Concern for appearance • Tendency toward vegetarianism	• Revised Diabetes Eating Problem Survey (DEPS-R) • Modified SCOFF (mSCOFF) test • Single question "Have you ever been overweight?"

Disordered eating in young people with diabetes is associated with short-term and long-term complications such as DKA, abnormal lipid profiles, retinopathy, and neuropathy.[230]

Clinicians working with young people with diabetes and ED need to consider the following in planning interventions: insulin regimen and potential for omission, glycemic targets, energy requirements, potential for food and insulin manipulation, body dissatisfaction, family functioning, exercise type and frequency, binge eating behaviors, potential laxative abuse and sleeping patterns.

An interdisciplinary approach to treatment is considered the standard of care for both ED and diabetes. Close liaison with the Specialist Eating Disorder team is required[231] with a clear common weight goal for the person with diabetes. It is important that insulin adjustments by the diabetes team do not support binge eating or food avoidance behaviors. Supervision of insulin doses and family-based interventions are helpful strategies in treatment of disordered eating.[31] More research is needed for interventions to prevent and treat disordered eating in diabetes.

16 | RESEARCH

There is a need for further research in many areas of pediatric diabetes management and education, particularly in effective nutrition therapy interventions in relation to long-term outcomes,

newer technologies and hybrid closed loop (HCL) systems. There remains a lack of high-quality studies in many aspects of nutritional management.

17 | CONCLUSION

The nutritional care of children and young people with diabetes is complex. Diabetes management occurs within the context of the family, a surrounding social system, peer pressure, emerging independence, and the aim of maintaining quality of life. It requires a deep understanding of the relationship between treatment regimens and changing physiological requirements, including growth, fluctuations in appetite associated with changes in growth velocity, varying nutritional requirements and physical activity. Evidence suggests that it is possible to improve diabetes outcomes through attention to nutritional management and an individualized approach to education. This requires a clear focus on dietary goals in relation to glycemic outcomes and reduction in CVD risk. The foundation of successful dietary outcomes is the development of a trusting relationship between the child/adolescent and care providers, which facilitates behavioral change during the challenges of childhood and adolescent development.

ACKNOWLEDGMENTS

We would like to acknowledge the contributions of Dr Leena Priyambada for support with referencing of the chapter and the authors of the previous nutrition guideline chapters.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13429.

DATA AVAILABILITY STATEMENT

There is no original data linked to this guideline.

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How to cite this article: Annan SF, Higgins LA, Jelleryd E, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Nutritional management in children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(8):1297-1321. doi:10.1111/pedi.13429

Received: 24 October 2022 | Accepted: 27 October 2022

DOI: 10.1111/pedi.13443

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Assessment and management of hypoglycemia in children and adolescents with diabetes

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KEYWORDS: glucagon, hypoglycemia, impaired awareness of hypoglycemia

1 | WHAT IS NEW OR DIFFERENT?

- Updated recommendations of maximum permissible time in hypoglycemia, as defined by continuous glucose monitoring (CGM) metrics as well as details for treatment of hypoglycemia.
- Added descriptions of newer easy-to-use formulations of glucagon approved for use, which have variable availability across different regions of the world.
- Updated details from studies of newer insulin analogues and technology (CGM and advances in hybrid closed-loop therapy) on reducing the time spent in hypoglycemia.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Hypoglycemia and fear of hypoglycemia (FOH) are major physiological and psychological barriers to achieving optimal glycemia and may result in significant emotional morbidity for children with type 1 diabetes (T1D) and their caregivers. **B**
- Monitoring for hypoglycemia is a key component of diabetes care as is education about its causes, prevention, and treatment. Hypoglycemia is detected by self-monitoring of blood glucose (SMBG) or CGM. **A**
- Hypoglycemic events include all episodes of a plasma glucose concentration low enough to cause symptoms and/or signs, including

impaired brain functioning and expose the individual to potential harm. While there is no single numerical definition of hypoglycemia, clinical thresholds have been defined to aid assessment. **E**

- Glucose value <3.9 mmol/L (70 mg/dl) is used as the clinical alert or threshold value for initiating treatment for hypoglycemia because of the potential for glucose to fall further and avoid consequences of glucose levels below 3 mmol/L. Children with T1D should spend less than 4% of their time <3.9 mmol/L (70 mg/dl). **E**
- Glucose value <3.0 mmol/L (54 mg/dl) is defined as clinically important or serious hypoglycemia as neurogenic symptoms and cognitive dysfunction can occur below this level. Children with T1D should spend less than 1% of their time <3.0 mmol/L (54 mg/dl). **E**

- Severe hypoglycemia is defined as an event with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to administer carbohydrates, glucagon, or intravenous dextrose. Hypoglycemic coma is a subgroup of severe hypoglycemia defined as an event associated with a seizure or loss of consciousness. **E**
- The incidence of hypoglycemic coma has fallen over the last two decades with a current rate of 3 to 7 per 100 patient-years across international registries from developed countries. Although lower glycated hemoglobin (HbA1c) was considered a risk factor for severe hypoglycemia, this association is no longer observed with contemporary intensive insulin therapy. **B**
- Symptoms of hypoglycemia in the young result from adrenergic activation (shakiness, pounding heart, sweatiness) and neuroglycopenia (headache, drowsiness, difficulty in concentrating). In young children, behavioral changes such as irritability, agitation, quietness, and tantrums may be prominent. **B**
- Symptoms of hypoglycemia and physiological hormone responses may occur at a higher glucose level in children compared to adults. Thresholds for activation of hormonal responses may be altered by chronic hyperglycemia (i.e., occur at a higher glucose level) or repeated hypoglycemia (i.e., occur at a lower glucose level). **B**
- Common precipitants for hypoglycemia include excessive insulin dose, missed meals, exercise, sleep, and in adolescents, alcohol ingestion. Risk factors include previous severe hypoglycemic events and reduced hypoglycemia awareness. **B**
- Hypoglycemia with exercise may occur at the time of activity or may be delayed. **B** Education focused on insulin adjustment with exercise should be provided to enable people with T1D to exercise safely and avoid hypoglycemia.
- Glucose levels are recommended to be monitored overnight particularly if there is an additional risk factor that may predispose to nocturnal hypoglycemia. **E**
- Impaired hypoglycemia awareness can occur in children with diabetes and when present, is associated with a significantly increased risk of severe hypoglycemia. The determination of hypoglycemia awareness should be a component of routine clinical review. Impaired awareness may be corrected by avoidance of hypoglycemia. **B**

Treatment of hypoglycemia

- Hypoglycemia can be detected using SMBG or CGM. Newer factory-calibrated CGM devices are approved to make diabetes-related decisions. However, a blood glucose test is recommended if there is a suspected mismatch between clinical expectations and the sensor glucose level. Likewise, glucose should always be measured if the child is symptomatic or shows signs of hypoglycemia. **B**
- Hypoglycemia should be treated with oral glucose. An immediate source of glucose must always be available to young people with diabetes. Depending on circumstances, rapid-acting glucose should be followed by additional carbohydrates to prevent recurrence of hypoglycemia. **B**
- Treatment of hypoglycemia should increase blood glucose level by ~3 to 4 mmol/L (54 to 72 mg/dl). This can be accomplished by administering ~0.3 g/kg glucose orally, which equates to 9 g of glucose for a 30 kg child and 15 g for children >50 kg. **C**
- If on automated insulin delivery systems, the current approach of standard hypoglycemia management can cause rebound hyperglycemia, and hence consideration should be given to treat hypoglycemia with less glucose (e.g., 5 to 10 grams). **E**
- Following initial hypoglycemia treatment, blood glucose should be retested in 15 min. If there is no response or an inadequate response, repeat hypoglycemia treatment. Retest glucose in another 15 min to confirm that target glucose has been reached. **E**
- If on standard pump therapy (no suspend or automated insulin delivery) and glucose level <3 mmol/L, suspend insulin delivery until glucose >4 mmol/L. **E**
- Severe hypoglycemia requires urgent treatment.
  - In the ambulatory setting, SC or IM glucagon should be given (1 mg for children >25 kg and 0.5 mg for children <25 kg. Other preparations, more recently introduced and are easier to administer, including a single 3 mg dose of nasal glucagon for children >4 years, dasiglucagon, a stable glucagon analog, available as 0.6 mg ready-to-use pen SC for children ≥6 years and Gvoke (stable liquid glucagon) 0.5 or 1 mg autoinjector for children >2 years of age. **A**
  - In a hospital setting, intravenous glucose (10% dextrose, 2 ml/kg) can be administered. **B**
- Glucagon should be readily accessible to all parents and caregivers. Education on the technique of administration of glucagon is essential. **E**.

Prevention of hypoglycemia

- Hypoglycemia should be prevented, as it is often associated with significant psychosocial dysfunction. It can rarely lead to long-term sequelae and may be potentially life-threatening. **A**
- Diabetes education is critical in the prevention of hypoglycemia. **A**.
- Education about the risk factors for hypoglycemia should be given to children and their families to alert them as to times and

situations when increased glucose monitoring is required and when treatment regimens need to be changed. **E**

- Particular attention should be given to training children, parents, school teachers, and other caregivers to recognize the early warning signs of hypoglycemia and treat low blood glucose immediately and appropriately. **E**
- Devices for blood glucose measurement must be available to all children with diabetes for immediate confirmation and safe management of hypoglycemia. **E**
- Glucose monitoring should be performed prior to exercise, and extra carbohydrates may be consumed based on the glucose level and the expected intensity and duration of exercise. **B**
- Children and their parents should be trained to contact their diabetes care provider if hypoglycemia is documented without symptoms or if the symptoms are those of neuroglycopenia and not autonomic symptoms (i.e., impaired hypoglycemia awareness). **E**
- Regular screening for FOH is important to understand who will need interventions through educational and/or behavioral strategies, although evidence in children is limited. **E**
- Blood glucose goals may need to be adjusted upwards in children with recurrent hypoglycemia and/or impaired hypoglycemia awareness. **B**
- If unexplained hypoglycemia is frequent, evaluation for unrecognized celiac and Addison's disease should be considered. **E**
- Children and adolescents with diabetes should wear some form of identification or alert indicating that they have T1D. **E**
- Currently available technologies like CGM, automated insulin suspensions (Low Glucose Suspend, Predictive Low Glucose Suspend) and hybrid closed loop systems have reduced the duration of hypoglycemia. **A**

3 | INTRODUCTION

Hypoglycemia is a common occurrence in the management of T1D. It interferes with daily activities and poses a constant perceived threat to the individual and their families. It is a recognized limiting factor in achieving optimal glycemia[1] with an impact on quality of life.[2] Minimizing hypoglycemia is an important objective of diabetes management that can be addressed by acknowledging the problem, evaluating the risk factors and applying the principles of intensive glycemic management.[3] Therefore, it is vital to address this important clinical concern during diabetes education and institute appropriate management. The last two decades have experienced a paradigm shift in diabetes management through the availability of improved insulin analogues, insulin pump therapy and advent of CGM with algorithms incorporated in sensor-augmented pump therapy (SAP) to reduce and prevent hypoglycemia. There is increasing evidence to suggest that the time spent in hypoglycemia[4–6] and the rates of severe hypoglycemia have declined in recent years in developed countries with newer intensive therapies.[7–11] Unfortunately, hypoglycemia continues to be a problem in countries with limited resources, where many children are treated with insulin injections, with minimal access to technology and resources.

4 | DEFINITION AND INCIDENCE

4.1 | Definition

Hypoglycemic events include all episodes of a plasma glucose concentration low enough to cause symptoms and/or signs, including impaired brain functioning and expose the individual to potential harm. It is difficult to assign a numerical value to hypoglycemia. Nonetheless, it is important to identify and record a level of hypoglycemia that needs to be avoided because of its immediate and long-term impact on the individual. The definitions as below, incorporated in Table 1, are intended to guide clinical care and reporting and are based on glucose values detected by SMBG, CGM or a laboratory measurement of plasma glucose.[12] These definitions have informed the standardization of CGM metrics to set clinical targets for CGM data interpretation.[13]

1. *Clinical hypoglycemia alert*

A glucose value of <3.9 mmol/L (70 mg/dl) is an alert value that requires attention to prevent more serious hypoglycemia. The alert can be used as the threshold value for identifying and treating hypoglycemia in children with diabetes because of the potential for glucose levels to drop further.

2. *Clinically important or serious hypoglycemia*

A glucose value of <3.0 mmol/L (54 mg/dl) indicates clinically important or serious hypoglycemia. These low levels may lead to defective hormonal counter regulation[14] and impaired awareness of hypoglycemia (IAH). Neurogenic symptoms and cognitive dysfunction occur below this level[15,16] with subsequent increased risk of severe hypoglycemia. This level should be recorded in routine clinical care and reported in audits and in clinical trials of interventions directed toward reducing hypoglycemia.

3. *Severe hypoglycemia*

Severe hypoglycemia is defined as an event associated with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to administer carbohydrates, glucagon, or administer IV dextrose. This aligns with the definition of severe hypoglycemia in adults in accordance with the American Diabetes Association (ADA) guidelines.[17] This will also enable complete recording of events. Furthermore, if severe hypoglycemia is defined by coma or convulsions alone, the frequency of severe hypoglycemia in children can be underestimated. However, as young children require assistance to correct even mild hypoglycemia, the event requires an assessment by the caregiver and clinician as to the presence (or not) of hypoglycemia-induced cognitive dysfunction. A subgroup of severe hypoglycemia is *hypoglycemic coma* which is described as a severe hypoglycemic event resulting in coma or convulsion requiring parenteral therapy. These events should be recorded independently as these are unequivocally significant clinical outcomes.

4.2 | Incidence

The exact incidence of hypoglycemia is difficult to ascertain but mild hypoglycemia is common. Asymptomatic events are more likely to be

TABLE 1 Definition of hypoglycemia and clinical targets for CGM data[13]

Definition	*Clinical hypoglycemia alert*	*Clinically important or serious hypoglycemia*	*Severe hypoglycemia* Coma/convulsions/ severe cognitive impairment
Threshold	< 3.9 mmol/L or < 70 mg/dl	<3.0 mmol/L or < 54 mg/dl	No specific glucose threshold
Action	Requires hypoglycemia treatment	Requires hypoglycemia treatment	Requires third-party assistance to administer carbohydrates, glucagon, or intravenous dextrose
Acceptable CGM targets for hypoglycemia	<4% or <1 h/day	<1% or < 15 min/day	-

unrecognized and underreported while symptomatic hypoglycemia occurs on an average of two episodes per week with multiple such episodes in the lifetime.[18] The ADA workgroup on hypoglycemia in 2005 recommended the reporting of both the proportion (percentage) of people with T1D affected and the event rates (episodes per patient-year or 100 patient-years) for each of the categories of hypoglycemic events as these provide complementary information.[19]

Although there was a significant improvement in glycemia and reduction of diabetes-related complications in individuals with T1D on intensive glycemic therapy compared to conventional management in the Diabetes Control and Complications Trial (DCCT), there was a threefold increased risk of severe hypoglycemia events in individuals randomized to the intensive management arm of the study.[20] The incidence of severe hypoglycemia requiring treatment assistance was 61 per 100 patient-years in intensively treated versus 19 per 100 patient-years in those conventionally treated with an incidence of coma and/or seizure of 16 per 100 patient-years and 5 per 100 patient-years, respectively. Similar high rates were reported in observational cohorts in Western Australia[21] and Colorado.[22] Historically, these high rates of severe hypoglycemia were associated with lower HbA1c[20–24] although this relationship weakened with time.[25,26] Significant reduction in the frequency of severe hypoglycemia was observed in Germany and Austria (Diabetes-Patienten-Verlaufsdokumentation—DPV), Western Australia, and Denmark with minimal/no association of severe hypoglycemia with glycemic status.[26–28] The incidence of hypoglycemic coma has fallen over the last two decades with a rate of 3 to 7 per 100 patient years across international registries.[29] The decreasing trends for the occurrence of severe hypoglycemia in youth have continued.[7–11] Unfortunately, hypoglycemia continues to be a problem in countries with limited resources as evidenced by high rates of severe hypoglycemia in Brazil[30] and India.[31] The cohorts in these studies were predominantly on insulin injections, with minimal access to technology and resources.

Younger age and low HbA1c were historical risk factors for severe hypoglycemia, however low HbA1c is no longer a strong predictor of severe hypoglycemia in pediatric T1D cohorts on contemporary therapy.[7,25,29,32,33] The T1D Exchange and the DPV registry did not find increased rates of hypoglycemic coma in those <6 years of age with HbA1c <7.5% (58.5 mmol/mol) compared with those with higher HbA1c levels.[32] No differences in HbA1c were also reported from an Indian study assessing children with or without severe hypoglycemia.[31] This change can be attributed to a number of factors including increased use of insulin analogues and insulin pump therapy,[27,34,35] and improved hypoglycemia education.[36] These studies highlight the important observation that optimal glycemia can be achieved without an increase in severe hypoglycemia.

5 | MORBIDITY AND MORTALITY WITH HYPOGLYCEMIA

5.1 | Mortality

In the pre- and immediate post-DCCT period up to more than a decade ago, hypoglycemia was assigned as the cause of death in 4%–10%[37–39] in population-based cohorts and international registries of childhood-onset diabetes. Most deaths attributed to hypoglycemia occurred in adults. Hypoglycemia can be difficult to ascertain with certainty as the cause of death.[40,41] The global burden of hypoglycemia-related mortality was ascertained from an analysis of death certificates from 109 countries from 2000 to 2014. The study reported global differences with high rates of hypoglycemia-related deaths in South and Central America and lower rates in Europe, North America, and Australasia.[42]

Hypoglycemia is also proposed to play a role in the "dead-in-bed" syndrome, which is more prevalent in people with T1D than in the general population. In a coroner's case series, dead-in-bed syndrome accounted for ~15% of deaths in young adult males (≤40 years) with diabetes.[43] Although the etiology is not well established, it has been postulated that it may be secondary to prolongation of QT interval caused by number of factors: acute hypoglycemia[44] on a background of autonomic neuropathy[45] and possible genetic influences.[46] In addition to hypoglycemia-induced abnormal QTc prolongation, hypokalemia and adrenergic activation increase the risk for ventricular arrhythmias.[47] Alterations in cardiac repolarization can lead to fatal ventricular arrhythmias and may contribute to the sudden nocturnal death of young individuals with T1D.[48] It is likely that widespread use of CGM and the increased use of population-based databases will clarify the true incidence of deaths caused by hypoglycemia in the future. Although the role of hypoglycemia in "dead-in-bed" syndrome remains unclear, it is important to recognize that this continues to be a source of distress for parents of children with diabetes.[49]

5.2 | Morbidity

Neurological sequelae of hypoglycemia

Previous studies have shown that early onset of diabetes predicts poorer cognitive function and hypoglycemia plays a critical role in causing brain dysfunction.[50] Severe hypoglycemia, particularly in children[51–53] under the age of 6 years, was associated with cognitive deficits and was believed to contribute to the neurotoxic milieu affecting brain development.[54] However, the role of acute hypoglycemia in causing long-term impairment has gained less traction, whereas repetitive, chronic hyperglycemia is now viewed as more injurious to the brain.[55]

Transient cognitive dysfunction occurs with hypoglycemia with recovery generally complete within 1 h of correcting glucose levels, although recovery from severe events can take up to 36 h.[56] The long-term implication of severe hypoglycemia on cognitive function was reported as part of the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up of the original DCCT cohort. There were no significant cognitive abnormalities observed even after 18 years in the entire cohort[57] and also among adolescents who participated in the trial,[58] while the 32-year follow-up demonstrated an overall decline in cognition with age.[59]

The association of structural brain abnormalities with severe hypoglycemia has received significant attention with neuropathological evidence suggesting that severe hypoglycemia may preferentially harm neurons in the medial temporal region, including the hippocampus.[60] Mesial temporal sclerosis,[61] larger hippocampal volumes,[62] and reduced gray and white matter volumes have been reported in children who experienced hypoglycemic seizures.[51] However, gray and white matter neurological changes are not seen only with hypoglycemia, but also in children with hyperglycemia.[63,64]

Psychological impact of hypoglycemia

Severe hypoglycemic episodes may have negative psychosocial consequences and undesirable compensatory behaviors arising from hypoglycemia.[65] These hypoglycemic symptoms can be distressing and embarrassing and impact academic, social, and physical activities. While this fear can induce anxiety, avoidance of these episodes may be adaptive, leading to appropriate vigilance in glucose management. Elevated levels of anxiety can lead to disruptions in daily activities impacting diabetes management.[66] This FOH impacts the child and family unit. The strongest predictor of parental FOH across studies is the experience of a severe hypoglycemic event with their child.[66] Given the negative consequences associated with severe hypoglycemic episodes, individuals with T1D and their parents are at risk for increased anxiety, poor sleep, and reduced quality of life.[2,67–69] FOH may lead families and/or physicians to accept higher glucose levels with behaviors directed toward avoiding hypoglycemia leading to suboptimal glycemic status.[2,70–72] A progressive and lasting increase in HbA1c occurs with episodes of severe hypoglycemia, contributing to an increase in long-term complications.[73] Routine FOH screening is important to recognize those who would benefit from intervention.[66] The Hypoglycemia Fear Survey (HFS) has been adapted for use for parents of young children,[74,75] as well as adolescents and children.[76] The Children's Hypoglycemia Index (CHI), developed independently of the HFS, has the added benefit of including a scale assessing FOH in specific situations, such as only at night or only at school.[77]

Behavioral interventions (cognitive behavioral therapy) and psychoeducation have been shown to reduce FOH in adults; this intervention may be of benefit in older children but pediatric studies are not available.[66] Pilot data, using a group-based behavioral intervention in caregivers of children with diabetes reduced FOH and parenting stress.[78] Apart from the behavioral intervention, the availability of real-time CGM[79] and algorithms with automated insulin suspension and delivery[4,80] has the potential to reduce FOH, although studies are limited in this field.

TABLE 2 Hypoglycemia signs and symptoms

Autonomic signs and symptoms
Shakiness
Sweatiness
Trembling
Palpitations
Pallor
Neuroglycopenic signs and symptoms
Poor concentration
Blurred or double vision
Disturbed color vision
Difficulty hearing
Slurred speech
Poor judgment and confusion
Problems with short-term memory
Weakness
Numbness
Dizziness
Lack of coordination and unsteady gait
Loss of consciousness
Seizure
Behavioral signs and symptoms
Irritability
Erratic behavior
Agitation
Nightmares
Inconsolable crying
Nonspecific symptoms
Hunger
Headache
Nausea
Tiredness

6 | SIGNS AND SYMPTOMS

Hypoglycemia is often accompanied by signs and symptoms of autonomic (adrenergic) activation and/or neurological dysfunction from glucose deprivation in the brain (neuroglycopenia),[81] as shown in Table 2. As the blood glucose concentration falls, initial symptoms result from activation of the autonomic nervous system and include shakiness, sweating, pallor, and palpitations. In healthy individuals without diabetes, these symptoms occur at a blood glucose level of ~3.9 mmol/L in children and 3.2 mmol/L in adults.[82] However, this threshold in individuals with diabetes will depend on their glycemic levels[83–86] with an adaptive shift of the glycemic threshold for symptom onset to a higher glucose level with chronic hyperglycemia and lower glucose level with chronic hypoglycemia. Neuroglycopenic symptoms result from brain glucose deprivation and include headache, difficulty concentrating, blurred vision, difficulty hearing, slurred speech, and confusion. Behavioral changes such as irritability, agitation, quietness, stubbornness, and tantrums may be the prominent symptoms particularly for the preschool child, and may result from a combination of neuroglycopenic and autonomic responses.[87] In this younger age group, observed signs are more important, and at all ages there is a difference between reported and observed symptoms or signs. The dominant symptoms of hypoglycemia tend to differ depending on age, with neuroglycopenia more common than autonomic symptoms in the young.[88]

Physiological responses in children and adolescents

It is well recognized that although many physiological responses are similar across the age groups, there can be significant developmental and age-related differences in children and adolescents. The DCCT reported a higher rate of severe hypoglycemia in adolescents as compared to adults; 86 versus 57 events requiring assistance per 100 patient-years[20] despite higher HbA1c in adolescents. Several physiological and behavioral mechanisms may contribute to this difference. Firstly, there are behavioral factors such as variable engagement with diabetes care which are associated with sub-optimal glycemia in adolescents.[89] Secondly, during puberty, adolescents with or without T1D are more insulin resistant than adults.[90] Adolescents also have quantitative differences in counter regulatory hormone responses. In healthy individuals without diabetes, hypoglycemia symptoms occur at a blood glucose level of ~3.9 mmol/L in adolescents and 3.2 mmol/L in adults[82] In adolescents with suboptimal glycemia, this glucose level may be higher, reported at 4.9 mmol/L in one study.[82] Intensively treated young adults with T1D counter-regulate and experience hypoglycemia symptoms at a lower glucose level than those on treatment with twice daily injections.[85] To date, nearly all studies have been conducted in adolescents and young adults primarily due to difficulty in studying a younger age group. As a result, little is known about responses in pre-adolescents as to whether younger children demonstrate a similar or different response to hypoglycemia although there is evidence that a developing brain is more susceptible to the influence of glycemic excursions.[91]

7 | HYPOGLYCEMIA AWARENESS

In healthy individuals without diabetes, endogenous insulin secretion is shut down and counter regulatory hormones (glucagon, epinephrine, and norepinephrine) are released in response to hypoglycemia.[92] However, in people with diabetes, there is a progressive loss of glucagon response to insulin-induced hypoglycemia. This has been demonstrated as early as 12 months after diabetes onset and is lost in most people with T1D by 5 years.[93,94] Individuals with diabetes are therefore primarily dependent on the epinephrine response to counteract the hypoglycemic effect of insulin. Recurrent episodes of hypoglycemia contribute to the development of defective counter regulatory hormone responses to subsequent reductions in glucose levels and may further exacerbate the problem, whereby "hypoglycemia begets hypoglycemia."

IAH is a syndrome in which the ability to detect hypoglycemia is diminished or absent, reported in ~25% of adults with T1D.[92] In children and adolescents, a similarly high prevalence (33%) of IAH was reported in 2002, which declined to 21% in 2015.[95,96] Although the prevalence of IAH has decreased, it remains a concern in a substantial proportion of adolescents.

IAH is associated with lowering of glycemic thresholds for the release of counter regulatory hormones and generation of symptoms. A two to threefold reduction in the epinephrine responses contributes to the impaired adrenergic warning symptoms during hypoglycemia.[97] Clinically, this is manifested as loss of some of the symptoms of hypoglycemia over time. The loss of autonomic symptoms precedes the neuroglycopenic symptoms and individuals are less likely to seek treatment for low blood glucose levels. As the awareness of low blood glucose level is impaired, hypoglycemia is prolonged. These episodes, if unrecognized and prolonged, can lead to seizures.[98] Individuals with IAH have a sixfold increase in severe hypoglycemic episodes.[99] This highlights the need to evaluate for IAH as part of clinical management. The identification of IAH is limited by the availability of tools to measure hypoglycemia awareness. It is not practical to measure the adrenergic responses during hypoglycemia to identify IAH and questionnaires have been developed as surrogate measures that can be administered to older children who are able to self-report. The single-question Gold,[99] the eight-question Clarke[100] and six-question modified Clarke[95,96] have been used to screen children with IAH (Appendices A to C). The Clarke questionnaire has higher specificity than Gold in predicting clinically significant hypoglycemia.[101,102] Although a score of ≥4 implies IAH on these measures, it is important to acknowledge that IAH is not an "all or none phenomenon" but reflects a continuum in which differing degrees of impaired awareness can occur.

The blood glucose threshold for activation of autonomic signs and symptoms is related to glycemic status, antecedent hypoglycemia, antecedent exercise, and sleep. Tight glycemic management leads to adaptations that impair counter regulatory responses[103] with a lower glucose level required to elicit an epinephrine response.[86] An episode of antecedent hypoglycemia may reduce the symptomatic and autonomic response to subsequent hypoglycemia, which in turn further

increases the risk of subsequent severe hypoglycemia.[104] Likewise, moderate-intensity exercise also blunts the hormonal response to subsequent hypoglycemia.[105] Most severe episodes of hypoglycemia occur at night as sleep further impairs the counter regulatory hormone responses to hypoglycemia in people with diabetes and in normal subjects.[106] On the other hand, the blood glucose threshold for neuroglycopenia does not appear to vary as much with the level of glycemia or with antecedent hypoglycemia.[82,107,108] The glycemic threshold for cognitive dysfunction may be triggered before autonomic activation and hence are the symptoms associated with IAH.

The cause of IAH is not well understood. "Hypoglycemia-associated autonomic failure" resulting from a failure of centrally-mediated counter regulation is one of the proposed mechanisms[109] although the term may be misleading as the autonomic system does not fail. Rather, recurrent hypoglycemia causes a process of adaptation referred to as habituation; that is, IAH may represent a habituated response to hypoglycemia.[110,111] A habituated response can also be temporarily reversed by the introduction of a novel (heterotypic) stimulus (dishabituation). Preliminary results of a recent study demonstrated that a single burst of high-intensity exercise restored counter regulatory responses to hypoglycemia induced the following day in a rodent model[112] and in people with T1D and IAH.[113]

IAH can be reversed by avoiding hypoglycemia for two to three weeks[114] but this may be difficult to accomplish and, until recently, has not been practical in a clinical setting with current therapies. Therapeutic options are limited although some individuals benefit from structured education.[115] Technological advances could potentially have a role to play with the use of CGM,[116] SAPT with low glucose suspend functions[4,117] or hybrid closed loop systems.[118]

8 | RISK FACTORS FOR HYPOGLYCEMIA

Risk factors for hypoglycemia can be classified as modifiable and non-modifiable; most are modifiable. Younger age (due to the inability to communicate symptoms) and prolonged diabetes duration (due to its association with IAH) increase the risk of hypoglycemia. A higher risk of hypoglycemia has also been reported with limited access to private insurance and lack of nationalized schemes to access technology.[22] The main risk factor for hypoglycemia is a mismatch between administered insulin and consumed food. Insulin excess could result from increased doses due to poor understanding of insulin type and action, accidental delivery, reduced food intake or missed meals, and in situations where glucose utilization is increased (during exercise) or endogenous glucose production is decreased (after alcohol intake).

Recurrent hypoglycemia

Majority of children with T1D who experience severe hypoglycemia have isolated events; however, a few experience recurrent episodes. After an episode of severe hypoglycemia, the risk of recurrent severe hypoglycemia remains higher up to 4 years compared with children who have never experienced severe hypoglycemia.[73] When hypoglycemia is recurrent, it is important to exclude IAH and rule out coexisting autoimmune disorders like subclinical hypothyroidism,[119] celiac disease,[120] and Addison's disease.[121,122] Rarely, surreptitious self-administration of insulin causes repeated and unexplained severe hypoglycemia and should be considered as a sign of psychological distress[123,124] with underlying risk factors such as eating disorders (anorexia and bulimia) and depression. The clinical factors associated with an increased risk of hypoglycemia are shown in Table 3.

TABLE 3 Clinical factors associated with hypoglycemia

Precipitants
Excess insulin
Less food consumption
Exercise
Sleep
Alcohol ingestion
Risk factors
Impaired awareness of hypoglycemia
Previous severe hypoglycemia
Longer duration of diabetes
Co-morbidities
Coeliac disease
Addison's disease
Hypothyroidism
Psychological distress

Exercise

The glucose response to exercise is affected by many factors including the duration, intensity and type of exercise, the time of day when exercise is performed, plasma glucose, and insulin levels, and the availability of supplemental and stored carbohydrates.[125] The risk of hypoglycemia is increased during moderate-intensity exercise, immediately after as well as 7 to 11 h after exercise.[126] The pathophysiology of post-exercise-induced hypoglycemia is multifactorial, and includes increased insulin absorption, increased insulin sensitivity, increased peripheral glucose utilization with depletion of glycogen stores and exercise-induced counter regulatory hormone deficits. Furthermore, children on fixed insulin doses are at "triple jeopardy" for hypoglycemia on nights following exercise related to: increased peripheral glucose utilization with exercise, impaired counter regulatory hormone responses during sleep, and unchanged insulin concentrations related to the treatment regimen.[127] Treatment guidelines to help individuals exercise safely are updated in this edition of the ISPAD guidelines (See ISPAD 2022 Consensus Guidelines Chapter 14 for Exercise in Children and Adolescents with Diabetes).

Alcohol

Alcohol inhibits gluconeogenesis[128] and hypoglycemia may occur if there is an inadequate intake of carbohydrates. Furthermore, the symptoms of hypoglycemia may be masked by the intoxicating effects of alcohol. Even moderate consumption of ethanol may reduce hypoglycemia awareness and impair the counter regulatory response to insulin-induced hypoglycemia.[129] Apart from the acute effects, moderate consumption of alcohol in the evening is associated with

reduced nocturnal growth hormone secretion and may increase the risk of hypoglycemia on the subsequent morning.[130] Although an increase in insulin sensitivity with alcohol intake has been postulated, this remains inconclusive.[131]

Nocturnal hypoglycemia

The Juvenile Diabetes Research Foundation (JDRF) CGM study group in 2010 described frequent prolonged nocturnal hypoglycemia on 8.5% of nights in both children and adults but more prolonged episodes in children.[132] In this study, the mean time spent in nocturnal hypoglycemia (<60 mg/dl) was 81 min. Almost half of these episodes were undetected by caregivers or individuals with diabetes.[133,134] The counterregulatory responses to hypoglycemia are attenuated during sleep[106,135,136] and individuals with T1D are much less likely to be awakened by hypoglycemia than individuals without diabetes.[106] This is significant as prolonged nocturnal hypoglycemia can lead to seizures.[98] Nocturnal hypoglycemia should be suspected if pre-breakfast glucose is low, and/or the individual experiences confusion, nightmares or seizures during the night, or if impaired thinking, lethargy, altered mood, or headaches are reported on waking.[137] It is recommended to monitor overnight glucose levels, particularly if there is an additional risk factor that may predispose to nocturnal hypoglycemia. Younger age, lower HbA1c levels, antecedent exercise, and hypoglycemia are associated with a greater frequency of nocturnal hypoglycemia.[138]

Studies of overnight hypoglycemia in children have been unable to identify a glucose value that reliably predicts a low risk of hypoglycemia. In a study using CGM to detect nocturnal hypoglycemia, there was a twofold increase, 45% versus 22%, in the incidence of hypoglycemia with a bedtime glucose ≤5.5 mmol/L (100 mg/dl).[139] Similarly, the fasting glucose levels were significantly lower (6.6 mmol/L; 118 mg/dl) in those with than those without hypoglycemia (9.9 mmol/L; 179 mg/dl).[140] In contrast, in children on twice daily soluble and isophane (NPH) insulin therapy, hypoglycemia was partially predicted by a midnight glucose of <7.2 mmol/L (130 mg/dl).[141]

To reduce nocturnal hypoglycemia, a carbohydrate snack before bed for children on insulin injections was recommended based on studies using intermediate-acting insulins with peak action 4–12 h and duration 16–24 h.[142] However, use of long-acting insulin analogues such as glargine and detemir, due to their less pronounced peak effect, have reduced overnight hypoglycemia.[143] Hence, extra snacks may be unnecessary[144] and enforcing pre-bed meals may contribute to nocturnal hyperglycemia and add unnecessary calories contributing to weight gain. The recommendation for inclusion of pre-bed snacks is not mandatory and should be individually tailored.[144] Newer insulin analogues, like the ultralong-acting basal insulin degludec, have the potential to provide similar glycemia while reducing nocturnal hypoglycemia risk.[145]

Nocturnal hypoglycemia is less frequent with pump therapy and there has been a further decline with use of pumps that incorporate control algorithms that suspend basal insulin with sensor-detected,[146] sensor-predicted hypoglycemia[4] and hybrid closed loop systems.

9 | HYPOGLYCEMIA TREATMENT

Diabetes education should focus on recognition of precipitants and risk factors for hypoglycemia, the ability to detect subtle symptoms, the importance of confirming low glucose levels by monitoring, appropriate hypoglycemia treatment and approaches to prevent future events. Figure 1 outlines the management of hypoglycemia.

Hypoglycemia can be detected using SMBG or CGM. Newer factory calibrated CGM devices are approved to use sensor glucose data to make diabetes management decisions. However, a fingerpick blood glucose measurement is recommended if there is a suspected mismatch between clinical expectations and the sensor glucose level. Likewise, blood glucose should always be tested if the child is symptomatic or shows signs of hypoglycemia. If the glucose level is <3.9 mmol/L (70 mg/dl), remedial actions to prevent a further drop in glucose is recommended. In adults, 20 g of carbohydrate in the form of glucose tablets raised glucose levels by ~2.5 to 3.6 mmol/L (45–65 mg/dl) at 45 min.[147–149] This was extrapolated to 0.3 g/kg in children, which would be approximately 9 g of glucose for a 30 kg child and 15 g for a 50 kg child. A pediatric study has confirmed that 0.3 g/kg of rapidly acting carbohydrate containing preparations (glucose tablets, orange juice), effectively resolved hypoglycemia in most children and raised median blood glucose by 1–1.3 mmol/L in 10 min and 2–2.1 mmol/L in 15 min without rebound hyperglycemia at the next meal.[150] A similar weight-based approach was also found to be effective in children on insulin pumps.[151] In children on insulin pump therapy, it is also recommended that basal insulin delivery is suspended if glucose level is <3 mmol/L. To date no studies have looked at the amount of carbohydrate required to treat hypoglycemia in children who use automated insulin delivery systems that suspend basal insulin delivery when hypoglycemia is predicted or use closed loop systems. The current approach of standard hypoglycemia management can cause rebound hyperglycemia[152]; hence consideration should be given to treat hypoglycemia with less glucose (e.g., 5–10 g)[152,153] or approximately half the amount of glucose used for standard treatment.

The choice of carbohydrate source is an important consideration for hypoglycemia treatment. In clinical practice, glucose-containing products are recommended for immediate treatment because of their rapid absorption from the intestine. It is important to review the amount of glucose in the product to ensure adequate treatment is provided. When glucose tablets are not available, dietary sugars can be used. Glucose tablets result in a higher rate of relief of symptomatic hypoglycemia 15 min after ingestion compared with dietary sugars (hard candy, table sugar, jelly beans, fruit juice). If available, glucose-based treatment should be the first choice when treating symptomatic hypoglycemia.[154]

Although 15 g of "carbohydrates" are recommended for first-line treatment by ADA,[155] it is essential to note that the dose required for dietary sugars is not established and may be higher than glucose. For example, 40 g of carbohydrate in the form of juice results in approximately the same rise as 20 g in the form of glucose tablets.[147] Likewise, sucrose requires a greater amount to provide the same increase

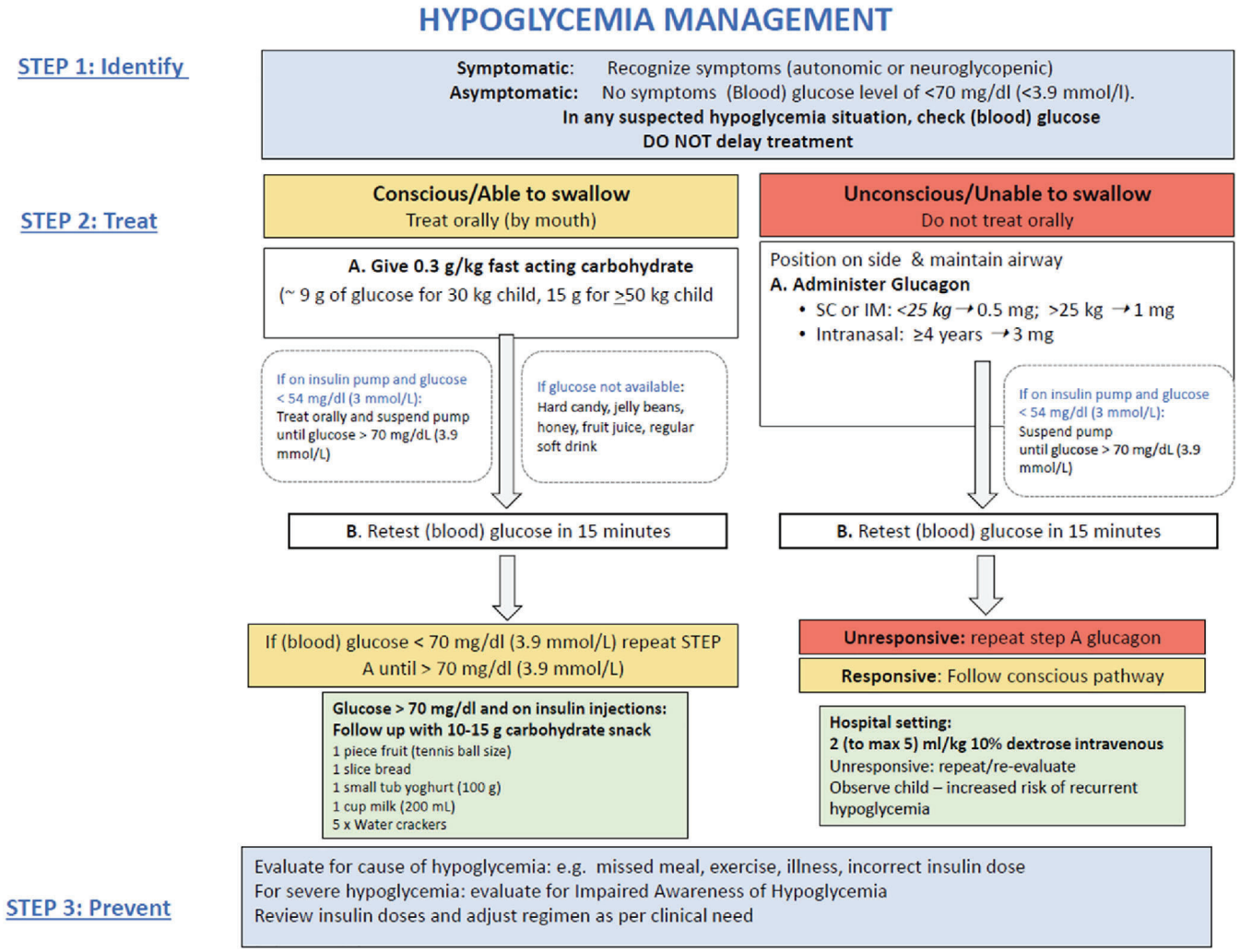

FIGURE 1 Hypoglycemia management

in blood glucose concentration compared to oral glucose.[148] Husband et al reported that glucose- and sucrose-based hypoglycemia treatments resulted in timely resolution of hypoglycemia, although fructose-based treatment (fruit juice) was less effective.[156] Honey and fruit juice have been reported to be more effective than one sugar cube (sucrose) for treatment of hypoglycemia.[157] Honey contains nearly 70% fructose and glucose as main sugars although composition differs depending on the geographical origin which may lead to variability in response. Jelly beans contain glucose syrup and although they cause glucose levels to rise, the resolution of hypoglycemia is slower.[150] If a soft drink is used for treatment, ensure regular and not sugar-free/diet forms is used for treatment.

Dietary sugars are generally discouraged to avoid confusion between "treatment" and "treats" with the potential of hypoglycemia induction to receive these treats. Furthermore, complex carbohydrates, or foods containing fat (chocolate) which delay intestinal absorption and result in slow absorption of glucose should be avoided as the initial treatment of hypoglycemia. Whole milk containing 20 g of carbohydrate (435 ml) causes a minimal response with rise of ~1 mmol/L (18 mg/dl).[147]

After treatment, repeat a blood glucose measurement after 15 min.[158] If there is no response or an inadequate response, repeat oral intake as above. It is important to be aware of the physiological time lag with rising and falling sensor glucose levels in children using CGM.[159] The decision to repeat hypoglycemia treatment should not be based on a low sensor glucose level at 15 min unless a finger prick glucose measurement confirms persistent hypoglycemia. Once hypoglycemia is reversed, the child should have the usual meal or snack if due at that time; otherwise, a snack (15 g) of slower-acting carbohydrate, such as bread, milk, biscuits, or fruit should be consumed. However, this is not always required, particularly for those on insulin pump therapy.

The amount of carbohydrate required to guide treatment will also depend on the size of the child, type of insulin therapy, active insulin on board, and the timing and intensity of antecedent exercise.[147,160] It is important to educate the child/caregiver to consider the factors that led to hypoglycemia.

Severe hypoglycemia

Severe hypoglycemia requires urgent treatment. If the child is unconscious or unable to swallow, hypoglycemia can be safely

TABLE 4 Available forms of glucagon for hypoglycemia treatment

Product	Preparation	Route	Dose	Ages
Glucagon	1 mg/ml lyophilized powder to be reconstituted with diluent	SC/IM	1 mg: children >25 kg 0.5 mg: children <25 kg	All ages
Baqsimi	3 mg glucagon nasal powder	Intranasal	3 mg	>4 years
Dasiglucagon	0.6 mg/0.6 ml prefilled syringe or autoinjector	SC	0.6 mg	≥6 years
Gvoke Hypopen	0.5, 1 mg prefilled syringe or autoinjector	SC	1 mg: children >45 kg 0.5 mg: children <45 kg	>2 years

reversed by administration of glucagon, a potent and effective agent that can be administered intravenously, intranasally, intramuscularly or subcutaneously.[161] Table 4 shows a list of the available forms of glucagon.

Recombinant crystalline glucagon is available as a lyophilized (freeze-dried) powder that is mixed with an aqueous diluent to a concentration of 1 mg/ml. Commercially available glucagon rescue kits include GlucaGen® HypoKit 1 mg (Novo Nordisk®A/S, Bagsvaerd, Denmark) and Glucagon Emergency Rescue Kit (Eli Lilly and Company, Indianapolis IN). The recommended glucagon dose is weight based: 1 mg for adults and children >25 kg and 0.5 mg for children <25 kg (according to Novo Nordisk manufacture guidelines) while Eli Lilly uses a weight cut-off of 20 kg. The evidence for these recommendations is unclear.

Glucagon often induces nausea and vomiting on regaining consciousness and hence it is important to continue close observation and glucose monitoring after treatment.[162] The frequency of side effects increases with repeated doses. The efficacy of glucagon depends on having adequate hepatic glycogen. Consequently, glucagon would be predicted to be less efficacious in cases of hypoglycemia associated with prolonged fasting; in these circumstances, parenteral glucose would be the therapy of choice.[162] Currently available preparations require glucagon reconstitution with sterile diluent and therefore parents and caregivers require instruction on how to prepare and administer glucagon. Because glucagon is seldom used, parents and caregivers require regular reviews about when and how to administer glucagon. The need for reinstitution of glucagon powder before use is a known challenge which can delay or prevent glucagon administration. To overcome this barrier, an intranasal single-use glucagon preparation is now available as a needle-free device that delivers glucagon for the treatment of severe hypoglycemia in children[163] and adults[164,165] with T1D. A recent meta-analysis indicated that intranasal glucagon and SC/IM glucagon were equally effective in resolution of hypoglycemia in conscious individuals.[166] Intranasal preparation may cause headache, upper airway discomfort, tearing, or nasal congestion in addition to the typical side effects of glucagon.[163] A single dose of 3 mg is used in children (≥4 years) and adults with T1D.[167] Administration of nasal glucagon is faster and has a much higher success rate for delivery of the full dose with fewer errors than injectable glucagon.[168] Recently, dasiglucagon has also received regulatory approval.[169] Dasiglucagon, a soluble and stable glucagon analog available as 0.6 mg ready-to-use pen, provided rapid and effective reversal of hypoglycemia in children (≥6 years)[170] and adults[171] with T1D; side-effects were comparable to IM glucagon. A premixed SC autoinjector Gvoke HypoPen® (liquid-stable glucagon) is also available for use in children >2 years of age.[172,173] The availability of different forms of glucagon varies across different regions of the world and access to these forms of hypoglycemia treatment may be limited in lower resource settings.

In a hospital setting, intravenous glucose or glucagon may be given. Intravenous glucose should be administered by trained personnel over several minutes to reverse hypoglycemia. The recommended dose is 0.2 g/kg of glucose which equates to 2 ml/kg of 10% dextrose with a maximum dose of 0.5 g/kg body (5 ml/kg). As high concentrations cause sclerosis of peripheral veins, the maximum concentration of dextrose that can be administered through a peripheral vein is 25% dextrose. Rapid administration or an excessive concentration (dextrose 50%) can result in a rapid osmotic change with risk of hyperosmolar cerebral injury.[174] 10% dextrose is effective and safe and hence recommended for management.[175] In the event of recurrent hypoglycemia, the child will require additional oral carbohydrates and/or intravenous infusion of 10% dextrose to provide a glucose infusion rate of 2–5 mg/kg/min (1.2–3.0 ml/kg/h). The predisposing events that led to the severe event should be evaluated to prevent future events. Caregivers need to be aware that following a severe hypoglycemic event, the child will be at higher risk of a future event, and alterations to insulin therapy may be appropriate.

Glucagon is not readily available in countries with limited resources. Sugar or any other powdery substance or thin liquids such as a glucose solution or honey should not be given forcibly to the semi/unconscious child. The child should be put in a lateral position to prevent aspiration and a thick paste of glucose (glucose powder with a few drops of water or crushed table sugar with consistency of thick cake icing) smeared onto the dependent cheek pad; the efficacy of this practice is anecdotal. Although an earlier study in healthy adult volunteers demonstrated poor buccal absorption of glucose,[176] sublingual glucose was found to be a child-friendly method of raising blood glucose in severely ill children with malaria.[177] In situations where there is a danger of aspiration and intravenous access is unavailable, parenteral glucose solutions may be administered via nasogastric tubes.[178]

Minidose glucagon

Children with gastrointestinal illness and/or poor oral carbohydrate intake with a blood glucose ≤4.4 mmol/L can benefit from mini-

dose glucagon injected by their caregivers to avoid impending hypoglycemia and hospitalizations.[161,179] The dose of reconstituted glucagon is administered subcutaneously using a 100 U insulin syringe (1 unit ~10 μg of glucagon) and is age-based: 2 units (20 μg) for children ≤2 years and 1 unit/year for children ≥3–15 years (with a maximum dose of 150 μg or 15 units). If blood glucose fails to rise over the first 30 min, a repeat injection should be given using twice the initial dose. The minidose glucagon regimen resulted in an increase of 3.3–5 mmol/L of glucose (60–90 mg/dl) within 30 min of administration with an average increase of 4.7 mmol/L.[161]

10 | ROLE OF TECHNOLOGY IN REDUCTION OF HYPOGLYCEMIA

The rapid technological advances in diabetes management with stand-alone CGM systems or systems with integrated CGM and insulin pump use have empowered individuals with T1D to further reduce the frequency of hypoglycemia. There are many technological devices available to reduce hypoglycemia; however, the choice of device should be a decision based on a dialogue between the health care professional and the individual with diabetes. More detailed recommendations and guidelines for pump and CGM are covered in ISPAD pump and CGM chapters respectively (See ISPAD 2022 Consensus Guideline Chapter 16 on Diabetes Technologies: Glucose Monitoring and Chapters 17 on Diabetes Technologies: Insulin delivery).

Continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion (CSII) use can reduce hypoglycemia. A meta-analysis showed that pump therapy in children may be better than injections in reducing the incidence of severe hypoglycemia.[180] Compared to injection therapy, a lower risk of severe hypoglycemia was associated with CSII in the T1D exchange,[181] DPV registry[182] and the International Pediatric SWEET Registry.[183]

Continuous glucose monitoring: Stand-alone systems

Studies have shown a reduction in time spent in hypoglycemia with a concomitant decrease in HbA1c with CGM use in both children and adults.[184–186] There was a trend to reduction in severe hypoglycemia in the DPV and T1D Exchange registry with CGM initiation.[8,181] Sensors with predictive alerts can further reduce hypoglycemia.[187] These alerts with real-time glucose monitoring may also contribute to reduced parental FOH.[79] Intermittently scanned CGM (isCGM) (without alerts) also has the potential to reduce hypoglycemia,[188] however the reduction in hypoglycemia is greater with real-time CGM than with intermittently scanned isCGM[189] and is potentially a better management tool for individuals at high risk of hypoglycemia.

Sensor-augmented pump therapy with low glucose and predictive low glucose suspension

The incorporation of algorithms in sensor-augmented pump therapy further reduces the time spent in hypoglycemia due to suspension of basal insulin delivery with hypoglycemia (Low Glucose Suspension)[117,190] and with prediction of hypoglycemia.[4,191] Predictive Low Glucose Management (PLGM) systems include the Medtronic PLGM system and Tandem Basal IQ. The Medtronic PLGM system suspends basal insulin when sensor glucose (SG) is at or within 3.9 mmol/L (70 mg/dl) above the patient-set low limit and is predicted to be 1.1 mmol/L (20 mg/dl) above this low limit in 30 min. Following pump suspension and in the absence of user interference, insulin infusion resumes after a maximum suspend period of 2 h or earlier if the auto-resumption parameters are met. Prospective and retrospective studies have shown that PLGM reduces hypoglycemia.[4–6,192,193] Time spent in hypoglycemia <3.5 mmol/L was reduced from 2.8% at baseline to 1.5% during the 6-month study compared with a reduction from 3% to 2.6% with SAPT, representing close to 50% reduction in hypoglycemia.[4]

The Tandem Basal IQ, available with Dexcom G6® CGM and Tandem t:slim X2 pump, uses a linear regression algorithm that relies on the last four SG values to predict SG level in 30 min. It suspends basal insulin when SG is predicted to be 4.4 mmol/L (80 mg/dl) in 30 min or current SG is <3.9 mmol/L (70 mg/dl). Time spent in hypoglycemia <3.9 mmol/L decreased from 3.6% at baseline to 2.6% during the 3-week PLGM period compared with 3.2% with SAPT, representing a 31% relative reduction in hypoglycemia.[191] The insulin resumption is more aggressive and hence there was no difference in the mean SG levels in the two groups or in the time spent in hyperglycemia.[191]

Hybrid closed-loop systems

Automated insulin delivery offers the potential to mitigate the significant glycemic excursions associated with conventional therapy. These systems utilize a control algorithm that automatically and continually increases and decreases the subcutaneous delivery of insulin based on real-time sensor glucose levels. Several systems are available but all may not have national regulatory approvals: Medtronic 670G/770G[194,195] and Medtronic 780G[196] with advanced algorithm is approved for use in children 7 years and above, Control IQ (Tandem Inc., San Diego, California)[197,198] for 6 years and above and CamAPS FX interoperable app[118,199–201] (CamDiab, Cambridge, UK) for 1 year and above. These hybrid closed-loop systems require user input of insulin bolus for meals ± corrections. Both in clinical trials and in observational studies, these systems have consistently shown a reduction in time spent in hypoglycemia while improving time in target glucose range.[194,195,197,202,203] Improved glycemic variability, especially overnight, with reduced hypoglycemia has the potential to improve sleep and quality of life in children and their parents.[204] Individuals with IAH also have the potential to improve their hypoglycemia awareness with these systems.[118] Use of closed loop systems in individuals with IAH showed reduction in hypoglycemia with higher self-reported hypoglycemia scores during controlled hypoglycemia. However, this was not associated with an improvement in counter regulatory hormonal responses which could be due to the relatively short duration (8 weeks) use of the system.[118] Advancements in this field are ongoing in the pursuit of a fully automated closed loop system that can further improve glycemic outcomes and reduce the burden of disease in individuals with T1D.

11 | SUMMARY

Diabetes management should optimize glycemia with minimal hypoglycemia to positively impact quality of life. Hypoglycemia education and management is fundamental in the care of children with T1D. This guideline provides an evidence-based approach to hypoglycemia management.

AUTHOR CONTRIBUTION

All authors contributed to the content of the chapter, reviewed and approved the final version of the manuscript.

ACKNOWLEDGEMENT

Open access publishing facilitated by The University of Western Australia, as part of the Wiley - The University of Western Australia agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

Dr Dovc received speaker's honoraria from Abbott, Pfizer, Novo Nordisk, and Eli Lilly and Advisory Board honoraria from Sanofi and Pfizer. Dr Dovc is a member of the European Commission Expert panel for Medical Devices for Endocrinology and Diabetes. Dr Abraham received speaker's honoraria for educational sessions organized by Medtronic Australia and Eli Lilly.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Abraham MB, Karges B, Dovc K, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(8):1322-1340. doi:10.1111/pedi.13443

APPENDIX A

A.1 | CLARKE'S HYPOGLYCAEMIA AWARENESS QUESTIONNAIRE

(Tick only one response for each question)

1. **Tick the category that best describes you.**
2. ☐ I always have symptoms when my blood sugar is low (A)
3. ☐ I sometimes have symptoms when my blood sugar is low (R)
4. ☐ I no longer have symptoms when my blood sugar is low (R)

Have you lost some of the symptoms that used to occur when your blood sugar was low?

☐ Yes (R)
☐ No (A)

In the past 6 months how often have you had moderate hypoglycemia episodes where you may have been confused, disorientated or lethargic, and needed help to treat yourself?

☐ Never (A)
☐ Once or twice (R)
☐ Every other month (R)
☐ Once a month (R)
☐ More than once a month (R)

In the past year, how often have you had severe hypoglycemic episodes, where you were unconscious or had a seizure and needed glucagon or intravenous glucose?

☐ Never (A)
☐ 1 to 3 times (R)
☐ 4 to 7 times (R)
☐ 8 to 11 times (R)
☐ 12 times or more (R)

5. **How often in the last month have you had readings < 70 mg/dl (<3.9 mmol/L) with symptoms?**
6. ☐ Never
7. ☐ 1 to 3 times in the month
   ☐ Once a week
   ☐ 2 to 3 times a week
   ☐ 4 to 5 times a week
   ☐ Almost every day

How often in the last month have you had readings < 70 mg/dl (<3.9 mmol/L) without symptoms?

☐ Never
☐ 1 to 3 times in the month
☐ Once a week
☐ 2 to 3 times a week
☐ 4 to 5 times a week
☐ Almost every day

Scoring Q5 and Q6:

R = answer to Q5 is less than answer to Q6

A = answer to Q5 is greater than or equal to answer to Q6

How low does your blood sugar go before you feel symptoms?

☐ 60–69 mg/dl or 3.3–3.8 mmol/L (A)
☐ 50–59 mg/dl or 2.8–3.3 mmol/L (A)
☐ 40–49 mg/dl or 2.2–2.7 mmol/L (R)
☐ <40 mg/dl or <2.2 mmol/L (R)

8. **To what extent can you tell by your symptoms that your blood sugar is low?**

☐ Never (R)
☐ Rarely (R)
☐ Sometimes (R)
☐ Often (A)
☐ Always (A)

Scoring

A = aware, R = reduced awareness, U = unaware

Four or more R responses = reduced awareness

Source: Adapted from Reference 205.

APPENDIX B

B.1 | MODIFIED CLARKE'S HYPOGLYCEMIA AWARENESS QUESTIONNAIRE

(Tick only one response for each question)

	1. **In the last month, how many times have you had a blood glucose level (BGL) of less than 3.5 mmol/L (63 mg/dl)?** ☐ None ☐ One to three times in the last month ☐ Once a week ☐ Two to three times a week ☐ More than three times a week
A = 0 PU = 1 U = 2	**In the last month, how many times have you tested and found a BGL less than 3.5 mmol/L (63 mg/dl) without realizing your BGL was low?** ☐ None ☐ One to four times ☐ Greater than four times
A = 0 PU = 1 U = 2	2. **Tick the box that best describes you.** I… ☐ always ☐ sometimes ☐ never ….have signs when my BGL is low.
U = 2 PU = 1 A = 0 A = 0	3. **How low does your BGL fall before you notice any signs?** ☐ Less than 2.5 mmol/L (45 mg/dl) ☐ 2.5–3.0 mmol/L (45–54 mg/dl) ☐ 3.0–3.5 mmol/L (54–63 mg/dl) ☐ Greater than 3.5 mmol/L (63 mg/dl)
U = 2 U = 2 PU = 1 PU = 1 A = 0	4. **Can you tell your BGL is low by certain signs or behavior?** ☐ Never ☐ Rarely ☐ Sometimes ☐ Usually ☐ Always
U = 2 A = 0	5. **Have you lost some of the signs and symptoms that used to occur when your BGL was low?** ☐ Yes ☐ No

Note: Questions 2 to 6 are scored A: Aware, PU: partially unaware, U: unaware. A score of ≥4 implies impaired awareness of hypoglycemia.
Source: Adapted from Reference 205.

APPENDIX C

C.1 | GOLD SCORE

Do you know when your hypos are commencing? (circle one only).

Always aware						Never aware
1	2	3	4	5	6	7

Note: A score of ≥4 implies impaired awareness of hypoglycemia.
Source: Adapted from Reference 99.

Accepted: 7 November 2022
DOI: 10.1111/pedi.13452

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Exercise in children and adolescents with diabetes

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1 | WHAT IS NEW OR DIFFERENT

- Since the previous guideline, progress has been made in the field of diabetes management and physical activity (PA).[1] An e-book that includes 10 articles on PA and type 1 diabetes (T1D) has been published[2] and the epidemiological evidence and gaps in knowledge and research in this book have been recently reviewed (Section 7).[3] Impact of age, sex, and physical fitness glucose responses to PA,[4] and a structured approach to exercise consultation (Section 4)[5] was presented. Finally, the benefits and limitations of technological advances in relation to PA were described in the same compilation.[6] Of note, many of the new data were derived from adult, rather than pediatric populations.
- This guideline incorporates a new theme focused on strategies for glucose management for athletes living with T1D based in part on a randomized controlled trial (RCT)[7] of the impact of acute hyperglycemia. General therapy recommendations for athletes[8] were described, and later a review regarding competitive athletes with T1D was published (Sections 6 and 9).[9]
- Several, technological developments since the last guideline in 2018 have been incorporated into these new guidelines (Section 8). Specifically, an international group released a position statement providing practical approaches for glucose management before, during, and after exercise using real-time continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) (Section 7).[10] Closed-loop systems have also been evaluated in the context of PA and in RCTs illustrating the first steps towards optimal glycemia in relation to PA (Section 8).[11–16]

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

This is a practical guideline aimed to be applied in both resource-rich as well as resource-limited settings (the latter is more comprehensively covered in the ISPAD 2022 Consensus Guidelines Chapter 25 on Management of children and adolescents with diabetes in limited resource settings). Exercise with diabetes is challenging to manage. The guidelines proposed, therefore, are meant as a starting point and should be tailored to the unique needs of each child and/or adolescent.

- Exercise is a cornerstone in the management and mitigation of cardiometabolic risk factors for children and adolescents with T1D and type 2 diabetes (T2D). Children and adolescents with T1D and T2D should be encouraged and supported to achieve the recommended 60 min of moderate to vigorous intensity PA every day. B
- Exercise is recommended to be regularly discussed as part of routine diabetes care for children and adolescents with T1D and T2D. E
- There is an increased risk of hypoglycemia during, shortly after, and up to 24 h after exercise due to increased insulin sensitivity. A
- A history of severe hypoglycemia in the preceding 24 h is generally a contraindication to exercise. A
- During all forms of physical exercise high glycemic index carbohydrates should be available to prevent and treat hypoglycemia. E
- Self-monitoring of blood glucose (SMBG), isCGM or CGM are essential for optimizing time in range and preventing hypoglycemia during and after exercise in all children and adolescents with diabetes. A
- Use of CGM during exercise is strongly recommended for children and adolescents with T1D, with CGM as the preferred modality to assist both user and guardian as symptoms of hypoglycemia and hyperglycemia may be difficult to detect. A
- CGM lags during prolonged aerobic exercise. It is recommended that glucose levels are confirmed by capillary fingerstick measurements if recent antecedent or present hypoglycemia is noted. A
- A wide range of insulin adjustment and nutrition strategies can be combined to keep the glucose level in the exercise range of 5.0–15.0 mmol/L or 90–270 mg/dl and prevent exercise induced-hypoglycemia. A
- Ketone levels, ideally measured using blood rather than urine, are generally recommended prior to exercise for children and adolescents with T1D if glucose values indicate possible insulin deficiency because elevated ketone levels before exercise pose a potential risk. D
- Exercise in children and adolescents with T1D and T2D is contraindicated in the presence of blood ketones ≥1.5 mmol/L or urine ketones: 2+ or 4.0 mmol/L. If blood ketone levels are between 0.6 and 1.4 mmol/L, exercise should be postponed until the cause of elevated ketone levels has been evaluated and an insulin bolus dose is given equal to half the usual individual correction dose (or 0.05 U/kg). B
- The type and amount of carbohydrates used in relation to exercise should be tailored to the specific activity. B
- Moderate intensity aerobic activity, such as walking and cycling for 15–45 min between meals, safely lower glucose levels >10.5 mmol/L (190 mg/dl). B
- Alcohol should be avoided before and during exercise as it may increase hypoglycemia risk, including nocturnal hypoglycemia after exercise, and impair performance. A
- Insulin should be administered in areas not actively engaged in muscle contraction. B
- Insulin dose adjustments are mostly required for aerobic exercise, and less likely required for very high intensity or anaerobic exercise which is more commonly associated with elevated glucose levels. A post-exercise insulin correction for hyperglycemia may be considered in such circumstances. B
- Recent technology advancements, including insulin pumps with hybrid closed loop (HCL) automated insulin delivery, provide benefits in relation to exercise for children and adolescents with T1D. Optimal use during exercise remains uncertain, and new systems will require individualized approaches, but the benefits of reduced hypo- and hyperglycemia after PA and specifically at night are clear. B
- Children and adolescents with T1D and T2D with significantly unstable diabetes, frequent severe diabetic complications (severe hypoglycemia, recurrent ketoacidosis) or advanced chronic complications of the disease should reduce or stop participating in vigorous exercise until metabolic control has improved and a specific exercise management plan has been made. High intensity exercise is generally contraindicated in those with more advanced or proliferative retinopathy. C

- An episode of severe hypoglycemia or recurrent antecedent hypoglycemia within the previous 24 h is a temporary contraindication to PA, C as is hyperglycemia ≥15.0 mmol/L (≥ 270 mg/dl) with concomitant ketonemia/ketonuria due to insulin deficiency, D acute injury or infection. C

Of note, many of the recommendations in this guideline are based on data derived from studies in adults with T1D. Therefore, practitioners and caregivers of children and adolescents should apply the evidence and adapt them where necessary based on local context. Furthermore, many of the studies have been conducted predominantly in male participants, and evidence cannot therefore be universally applied to females. Moreover, these recommendations are general, and it should be clarified that the physiological responses to exercise are individual, and thus optimal management might differ from individual to individual and context to context within the same person. These uncertainties are reflected in the grading above.

3 | INTRODUCTION

Regular PA is one of the cornerstones of diabetes management.[17,18] Despite this, over the years, PA levels in children have decreased in many countries with <10% of the global population of youth meeting the current 24-Hour Movement Guidelines.[19] In addition to reduced PA, an increase in body mass index (BMI) and declining oxygen uptake capacity (an indicator of physical fitness) have been reported in youth with T1D and T2D, leading to increased cardiovascular disease risk.[20–24] Consequently, these results require some form of action as the level of PA is often passed on from childhood into adulthood.[25,26]

There are clear physical and mental health benefits of regular PA for all youth. Therefore, current World Health Organization guidelines recommend that[27]

- Children and adolescents should do at least 60 min per day of moderate to vigorous-intensity, primarily aerobic, PA across the week.
- Vigorous intensity aerobic activities and activities that strengthen muscle and bone should be incorporated at least 3 days a week.
- Children and adolescents should limit the amount of time spent being sedentary, particularly the amount of recreational screen time.

It is not surprising that the benefits of PA have also been documented in children with chronic diseases.

There are many physical and mental health benefits of regular PA for youth with T1D and T2D including[28–35]:

- Lower HbA1c by approximately 0.3%–0.5% depending on baseline HbA1c level and the amount of PA, specifically in children and adolescents
- Lower risk of premature all-cause and cardiovascular mortality
- Increased cardiovascular and cardiorespiratory fitness
- Enhanced muscle mass and strength
- Reduced adiposity
- Increased bone mineral density
- Improved insulin sensitivity
- Improved cardiovascular risk profile
- Improved sense of overall well-being
- May extend remission time in children with new onset diabetes mellitus

Despite these benefits, very few individuals with or without diabetes meet the recommendations for PA. Children with T1D, younger than 7 years, engage in less daily PA than children without T1D of the same age.[36] Many adolescents with T1D,[37] and especially T2D,[38] have high rates of sedentary behavior and engage in less moderate to vigorous PA than youth without diabetes.[39] Thus, children and adolescents with diabetes may in general be less physically active than their peers.[39,40] In the general population, the reasons are multifactorial: lack of time, low motivation, access to facilities,[41,42] or disability.[43] The barriers for young people with diabetes are similar, but there are also many disease-specific barriers to manage. These include recurrent hypoglycemia and fear of hypoglycemia, elevated HbA1c and/or elevated glycemic variability, issues around body image, the planning required, parental hesitancy, social determinants of health, and general lack of knowledge in the field of exercise and diabetes.[44,45]

Incorporating regular exercise and PA into the lives of children and adolescents with diabetes is challenging as there is not a "one size fits all" approach. Health care professionals must feel confident in motivating and advising children and adolescents with diabetes and their caregivers to adopt and sustain a new behavior, have the necessary resources, and empower young people to incorporate PA and exercise into their daily lives and self-management plans. There are still many gaps in knowledge related to PA and pediatric diabetes. These include a lack of RCTs and large prospective cohort studies using adequate serial measurements, in individuals of different ages and sexes, that can elucidate appropriate "doses" of PA on diabetes-specific and general health-related outcomes. As new technologies become available, studies are also required to understand the impact of incorporating them into regular exercise and PA behaviors on cardiometabolic endpoints and psychological outcomes. Finally, in the current era of person-centered care and person-oriented research it is will be essential to involve individuals with diabetes, their partners, and caregivers when studies regarding PA and diabetes are planned and carried out.[3]

These guidelines cover many broad aspects of exercise and diabetes for children and adolescents with T1D and T2D. The recommendations are designed to serve as a starting point for health care professionals and allow progression to more detailed personalization of exercise management for specific exercise scenarios and diabetes management regimens.

4 | APPROACH TO CONSULTATION AND ASSISTANCE

The structured approach to the clinical consultation and planning of exercise for youth with diabetes requires a logical stepwise process. First, the

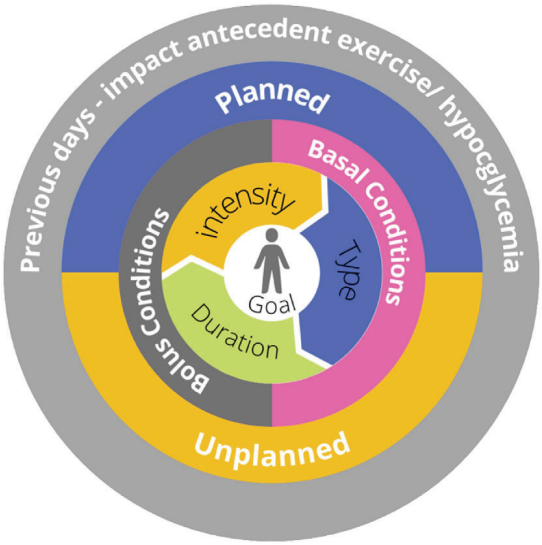

FIGURE 1 Structured approach to exercise consultations (original work by Chetty et al).[5] Copyright © 2019 Chetty, Shetty, Fournier, Adolfsson, Jones and Davis. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

dialogue starts with an exploration of personalized PA goals and a discussion about exercise physiology and expected glycemic excursions. The next step is to develop a methodical framework that encompasses glucose monitoring, insulin dosing strategy and fueling plan, to ensure safety and prevent hypoglycemia for youth with T1D.[5] For children and adolescents with T2D, exploring barriers and stage of change for increasing regular PA can help with co-designing individualized plans for behavior change.[46] Children and adolescents with T2D requiring insulin will need to discuss safely incorporating exercise into their dosing strategies. These templates may then be stratified to account for planned vs. unplanned exercise. The latter is associated with reduced flexibility to adjust insulin dose before exercise, thus necessarily emphasizing nutritional intake and vigilant glucose monitoring. The detailed evidence supporting specific insulin adjustments, nutrition/fueling, and glucose monitoring to guide exercise are discussed in the relevant sections below.

As many children with diabetes are sedentary, thoughtful planning is required to get started safely and sustain an active lifestyle in such situations. The following approach may be used for both habitually active and sedentary youth. The recommendation is to work outwards from the center of the "dartboard" in discussion with the young person with diabetes to develop an individualized plan (Figure 1).[5]

4.1 | Step 1: Setting and adjusting person-centered activity goals

Any clinical discussion must begin with a person-centered approach to exercise goals and motivation; clinicians may guide this discussion with individual-specific factors explored. These may include a desire for increased fitness, improved body composition, social inclusion such as peer activities or team sports, better glycemia, sports-specific high level or elite performance, and/or overall enjoyment.

Youth with T1D tend to be overweight[37,38] and most youth with T2D are overweight or obese.[47–49] Where improvements in body composition are sought, a strategy built around insulin dose reduction will reduce the need to prevent or treat hypoglycemia with extra carbohydrates. Additional attention should be paid in the initial consultation to known general barriers to exercise,[44,50–52] especially in adolescents, including personal barriers (self-motivation, motor skills, body image), social, environmental, and time factors.[53] In addition, psychosocial assessment and dietary advice should be included. Importantly, baseline fitness should be considered; lower baseline fitness is associated with greater glycemic variability in youth with T1D.[54] Youth with lower fitness will preferentially utilize muscle and liver glycogen stores (as a greater proportion of total energy expenditure) over fat oxidation Additionally, for the same amount of work performed, those less fit will necessarily be exercising at higher intensity, which is associated with risks of post-exercise hypoglycemia.[55] For athletes, education must also include planning for management during both training and competition. An athlete with newly diagnosed diabetes requires support to return to routine exercise as soon as possible. The information should then also be provided to the coach/trainer.

For children and adolescents with T1D participating in competitive sports, where optimal exercise performance is the goal, increased fueling for work performed together with an overall increase in both carbohydrate and protein intake across the day is likely required. Thus, insulin doses may need minimal adjustment or even need to be increased,[56] depending on the balance between the increase in nutritional intake and the improved insulin sensitivity from the higher overall intensity or volume of work performed. Dietitians should be closely involved in planning nutrition and the insulin doses required around an exercise training plan for children and adolescent athletes with T1D.

For many youth, the most uncomplicated goal is to foster participation and enjoyment of an active lifestyle. Hypoglycemia is well known to be associated with reduced exercise capacity. The impact of hyperglycemia remains less clear; the balance of evidence does not support a powerfully detrimental performance as a result of mild–moderate hyperglycemia.[7] Thus, hypoglycemia prevention and general safety should take precedence as the primary aim of the management plan. Where improved fitness also exists as a goal for a child or adolescent with T1D participating in competitive sport, the person, parent, and provider should discuss the anticipated improvements in insulin sensitivity that will likely occur over weeks and thus potential reductions in total daily insulin dose that may be needed, regardless of insulin regimen.

4.2 | Step 2: Discussion of exercise type

The type and duration of exercise will impact the expected acute glycemic excursions for children and adolescents with T1D, as discussed elsewhere in this chapter.[57] Predictable falls in blood glucose levels

(BGLs) should be incorporated into a plan based around general aerobic activity, with commensurate reductions in pre-exercise insulin dose and basal insulin exposure (where possible and with enough time for adjustments to be effective) together with a strategy to fuel appropriately. The risk of hypoglycemia also increases with exercise duration. Even at low intensity, prolonged exercise will inevitably require some adjustment of both insulin and fueling, which may be additive and progressive as activity extends.[58] Conversely, acute hyperglycemia may be seen with very high-intensity exercise, especially in fasted states. However, the glycemic response to bolus insulin and ingested carbohydrates is much less predictable. Persons with diabetes should be educated accordingly to anticipate this. Such acute hyperglycemia can be managed with either conservative correction doses[59] or components of low-intensity aerobic activity which increase glucose disposal without increasing the rate of glucose appearance, or cool-downs that lower serum lactate[60] and catecholamine levels. These acute excursions in BGLs are less likely to occur for adolescents with T2D.

4.3 | Step 3: Discussion of exercise timing and insulin action

In youth with T1D, and for some with T2D, exercise or general PA frequently occurs with some residual active insulin from a recent bolus ("insulin on board"). Examples include school sports, lunch breaks with playtime, after-school team practice, or generally spontaneous play. Thus, discussing insulin action time with youth and parents and how this impacts glycemic responses to exercise is crucial. Rapid-acting analogs generally attain peak action 60–100 min after injection, with a total duration of up to 5 h. It is ideal to manage glucose levels around exercise when minimal or no active rapid insulin is in the circulation. However, this is an uncommon scenario in youth who eat frequently and are unlikely to exercise before their first dose of prandial insulin of the day or several hours after their last meal or snack.

When exercise is planned to occur within 2–3 h of a meal, appropriate adjustment to the corresponding dose of pre-exercise insulin should be considered. General suggestions are delineated below based on clinical trial evidence in Tables A and B. Still, they will depend on whether the activity is predicted to cause a fall in BGL (see above, step 2) and the planned duration if known. Aggressive reductions of prandial insulin more than 90 min before exercise may reduce the risk of hypoglycemia during or immediately after exercise but may also be associated with hyperglycemia before exercise commences. Accordingly, these possible outcomes must be balanced and prioritized according to the personalized goals as set out and settled upon with the person with diabetes, as above in Step 1.

As fueling to maintain target glycemia during exercise is necessarily a function of the prevailing insulinemia, carbohydrate intake (as detailed later in this chapter) can be adjusted; less carbohydrate (in the range of 0.3–0.5 g/kg/h) is generally required when only basal insulin is active. In contrast, in adults double these amounts (or more) may be required when exercise coincides with peaking rapid-acting analog insulin.[57] It is important to discuss with the person that 0.3–0.5 g/kg/h may avoid hypoglycemia. Still, where optimal performance or maximal work is the desired goal, higher fuel intake is optimal. The approach is discussed in detail with specific recommendations below, and additional informative data are provided by glucose concentrations to fine-tune the fuel required.

When formulating a plan with youth and families, these same principles should be discussed by the diabetes team for planned activity. The time of day can then be discussed in detail, with clear evidence from several studies showing afternoon exercise of both low and high intensity is associated with more significant risks of delayed nocturnal hypoglycemia, frequently 7–11 h later.[61] This discussion can then be used to formulate the plan for any adjustments to the evening insulin dose, such as basal rate adjustments overnight[62] or the setting of predictive glucose suspension modes in those on pump therapy, or an adjustment to the evening basal analog in persons with diabetes on insulin injections, possibly by splitting the basal dose into two doses per day, where a reduction of the basal dose at night does not affect a whole day. At this point, individuals and their caregivers should be reminded that high intensity afternoon exercise that causes acute hyperglycemia is nonetheless associated with a risk of delayed nocturnal hypoglycemia. Therefore, exercise early in the day can be a strategy to reduce the risk of nocturnal hypoglycemia. There is a lack of evidence on best practice insulin advice for youth with T2D undertaking afternoon activity.

4.4 | Step 4: Contextualizing risks of hypoglycemia and safety considerations

Recent hypoglycemia prior to exercise is associated with an increased risk of further hypoglycemia (shown in adults)[63] due to attenuated counter-regulatory responses and glycogen depletion. A history of severe hypoglycemia in the preceding 24 h is generally a contraindication to exercise, while a background of hypoglycemia unawareness needs to be explored and included in a final action plan, as this may further increase the risk of hypoglycemia after exercise. In these individuals, extra fuel or greater insulin reductions should be discussed. This risk may be especially pertinent overnight during sleep, which is associated with impaired counter-regulation in youth with T1D.[64]

These discussions can logically lead to a discussion of glucose monitoring which is core to the optimal management of glucose levels during and after the event. CGM can provide data, including alerts, to inform incremental management, especially any need for carbohydrate intake to maintain optimal glucose levels, as discussed in detail below. In those not using CGM, BGL measurement should be performed as often as required, with management recommendations in Table 4 below based on a fingerstick BGL every 30 min.

4.5 | Step 5: Reviewing results and further adjustments to the plan

A follow-up consultation should be scheduled with persons living with diabetes and their families. This ideally provides an opportunity for

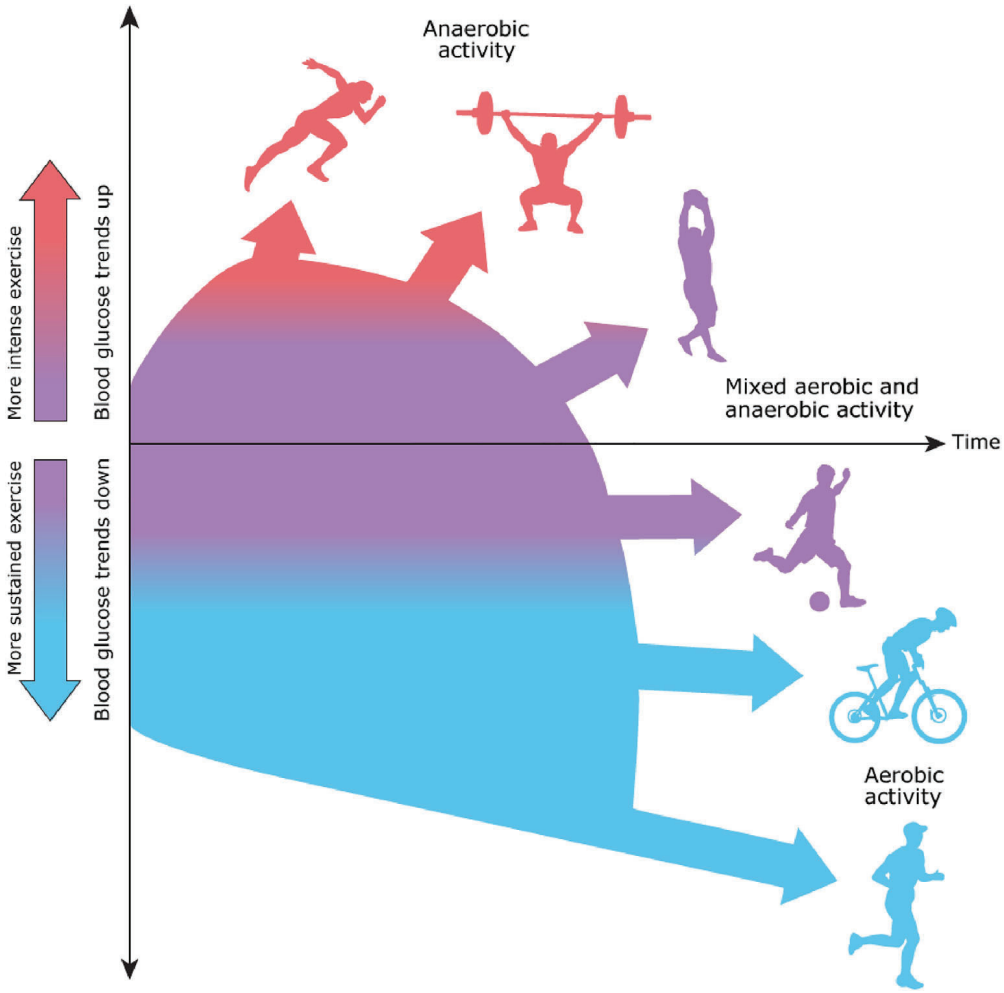

FIGURE 2 In general, aerobic exercise is associated with a drop in glycemia, while anaerobic and mixed forms of exercise can be associated with less of a drop or even a rise in glycemia. Individual responses are dependent on various additional factors, including the duration and intensity of the activity; initial blood glucose concentrations; individual fitness; time of day of exercise, concentrations of insulin, glucagon, and other counter-regulatory hormones in the circulation; and the nutritional status of the individual. Reproduced with permission from: Riddell MC. Management of exercise for children and adolescents with type 1 diabetes mellitus. In: UpToDate, Post-TW (Ed), UpToDate, Waltham, MA. (Accessed on August 2, 2022) Copyright © 2018 UpToDate, Inc.

further detailed sharing of information about insulin, fuel intake, and glucose levels before, during, and after exercise. Modern pump and CGM downloads make this rich information easily accessible to youth with diabetes and providers alike.

As acknowledged in the recommendations and tables below, any dose or fuel strategy should be considered as a starting point, as they are based on consensus and overall responses in clinical studies. Individual responses to exercise vary widely around these means,[65] and thus health care providers and people with diabetes must be prepared to modify and review a plan based on practical experience, as goals change (see Step 1), as children grow, as physical fitness improves or as the insulin replacement modality changes. Therefore, a clinical review cycle incorporating all these factors should occur as required, in the clinic setting, or more frequently if necessary or desired.

5 | PHYSIOLOGY

Exercise is considered a structured form of PA that can be classified as predominantly aerobic (oxidative metabolism) or anaerobic (non-oxidative metabolism) because of the major fuel systems used and how fuel is metabolized. With aerobic activities like walking, jogging, and cycling at a light to moderate intensity, heart rate and oxygen consumption increase from the resting state while lipids (i.e., free fatty acids and muscle triglycerides) and carbohydrates (blood glucose and muscle glycogen) are oxidized.[66] With brief anaerobic activities like sprinting and weightlifting, the skeletal muscle generates energy from anaerobic glycolysis, phosphocreatine, and free adenosine triphosphate.[66] Most forms of exercise, sport, play, and daily PA are a mix of aerobic and anaerobic metabolism. An understanding of the pathophysiology of exercise is valuable for the health care professional to be able to provide individualized advice to people living with diabetes, because of the complexity of exercise and diabetes.

Aerobic exercise tends to cause circulating glucose levels to drop,[65] while anaerobic or mixed forms of exercise are typically associated with an attenuated drop[67,68] or a rise in glycemia.[69] In general, mixed activities tend to have a moderating effect. However, several factors are thought to influence these general tendencies (Figure 2 and Table 1). The acute effects of anaerobic exercise on glycemia for youth with T2D are unclear.

5.1 | Aerobic exercise

The main determinants of glucose concentration in diabetes are nutrient intake, the timing of the meal, insulin concentrations in the

TABLE 1 Anticipated glucose response and physiological characteristics for people with type 1 diabetes undertaking aerobic, mixed, and anaerobic exercise.

Exercise type	Physiological characteristics	Effect on glucose level of person with type 1 diabetes[a]		Examples
Aerobic	Continuous moderate-intensity exercise predominantly below lactate threshold where glucose uptake by the muscles is greater than glucose output from the liver[65,101,106]	↘	↓	Running, walking, hiking, cycling, rowing, and swimming
Mixed with short intervals of anaerobic	Moderate-to-vigorous intensity (aerobic) activity interspersed with shorter (5–30 s) anaerobic bursts throughout[68,107]	↘	→	Basketball, football, soccer, cricket, handball, and martial arts
Mixed with long intervals of anaerobic	Low-to-moderate intensity (aerobic) activity interspersed with longer (10–180 s) anaerobic bursts throughout[108]	↗	→	Resistance training, circuit training, gymnastics, sprint training (running, swimming, rowing, cycling, etc.)
Anaerobic	Maximum effort exercise to fatigue (5 s–10 min) at an intensity above lactate threshold when glucose output from the liver is greater than uptake by the muscles[67,69]	↗	↑	500–2000 m row, 50–1500 m competition, 1–2 k cycle time trial, powerlifting
Competition day	Glucose output from the liver is likely to be exaggerated during competition leading to pronounced hyperglycemia compared to practice days	↑		Race, team, or individual game/match

[a]These are general trends that are also influenced by several other factors such as insulin on board (IOB), macronutrient intake, pre-exercise glucose level, antecedent exposure to hypoglycemia, fitness level, time of day, intensity and duration of exercise, training status, environmental conditions. Adult male data.[108] Adult male and female data.[68,69,107] Pediatric male data.[67] Pediatric male and female data.[65] This table was created with the assumption of low to moderate circulating IOB.

circulation, the rate of glucose production by the liver, and the rate of glucose utilization by the skeletal muscles and central nervous system.[9] In the fasted state, circulating glucose is predominantly determined by the amount of glucose released by the liver and the rate of glucose uptake into skeletal muscle and the brain.[70] The lower the circulating insulin concentrations and the higher the levels of glucose counter-regulatory hormones, the greater the glucose rate of appearance from the liver during aerobic exercise.[70] The volume of skeletal muscle engaged in exercise primarily determines the rate of glucose disposal. While skeletal muscle contractile actions increase the rate of glucose disposal during exercise via contraction-mediated GLUT 4 translocation to the sarcolemma, elevated catecholamine levels limit the uptake of glucose from the circulation to help prevent the drop in glycemia and increase the muscles' reliance on its glycogen stores as fuel.[66]

The contraction-induced translocation of the GLUT 4 transporter protein allows skeletal muscle to take up and utilize blood glucose as fuel even when insulin concentrations are extremely low.[71] However, low circulating insulin concentrations in T1D increases the rate of appearance of glucose from the liver[72] and ketone production,[73] which can be dangerous because this can cause severe hyperglycemia and dehydration ketoacidosis.

Because of the glucose-lowering action of aerobic exercise, exogenous insulin levels for children and adolescents with T1D should ideally be low to help prevent hypoglycemia.[58] Unfortunately, lowering insulin concentrations quickly is not possible, even with an insulin pump, so more proactive measures need to be taken. These may include a reduction in prandial insulin at the meal before exercise and/or a reduction in basal insulin delivery on the insulin pump[58] (see below for details). When insulin adjustments have not been made, increased carbohydrate consumption is the only option to prevent hypoglycemia[58] (see below for details).

5.2 | Very high intensity and anaerobic exercise

Anaerobic activities like sprinting, and weightlifting can cause glucose levels to rise, particularly if done early in the day with little to no prandial insulin in the circulation and if the activity is performed in isolation (i.e., without aerobic exercise), such as a 100-meter track event, a judo match, or a rowing sprint.[74] In addition, increased circulating concentrations of stress hormones associated with competition and intensive anaerobic exercise may augment the increase in glucose level, even before the event occurs. For example, Garry Hall Jr., who competed in the Sydney 2000 Olympic Games in sprint swimming (50-meter freestyle), raised his BGL to 300 mg/dl during his world record race that lasted over 21 s.

Because of the potential for glucose levels to rise with some forms of anaerobic exercise, insulin dose reductions are often not recommended, and post-exercise insulin correction for hyperglycemia may be considered[58] (see below for details).

5.3 | Mixed exercise

Most forms of PA for many youth consist of spontaneous play and/or team and field sports. These settings are often characterized by repeated bouts of relatively intense activity interspersed with low to moderate-intensity activity or rest.

This type of "interval" or "mixed" activity has been shown to result in a lesser rate of fall glycemia in persons with T1D compared to continuous moderate-intensity exercise, both during and after the event.[74] Mixed forms of exercise, therefore, may not require insulin dose adjustments.

5.4 | Reasons for dysglycemia during exercise in youth with T1D

The reasons for dysglycemia with exercise in diabetes are complex and multifaceted. The main factors associated with greater decreases in glycemia during aerobic exercise are likely the levels of circulating insulin and the exercise intensity and duration of the activity.[58] The levels of glucose counter-regulatory hormones (glucagon, catecholamines, cortisol, growth hormone) and the pre-exercise glucose level may also impact the change in glucose during aerobic exercise.[58] Additional factors, including an individual's physical size, muscle mass, age, sex, fitness level, stress levels and genetics, may also impact the change in glucose; however, the magnitude of these effects are less clear.

Exercise may increase the rate of absorption of subcutaneously delivered insulin,[75] which may increase insulin action soon after bolus administration. Insulin should be given in an area that is not actively engaged in muscle contraction. This may be difficult with some whole-body activities like swimming or when individuals have an insulin infusion set that is not easily moved for exercise. In addition, the impact of exercise on the absorption rate of ultra-long-acting basal insulin is unclear. However, one study in adults with T1D found that insulin detemir was associated with less hypoglycemia during and post-exercise.[76]

For youth with T2D, there is little evidence for the influence of duration, type, or intensity of exercise on acute glycemic excursions or glucose time-in-range. Cross-sectional studies suggest that more frequent bouts of structured PA,[77] particularly vigorous intensity structured activity[17] are associated with improved glycemia and cardiometabolic risk factors.

The unpredictable nature of activity in youth with T1D can make glycemic management challenging. Nonetheless, several strategies can be implemented to help limit dysglycemia associated with exercise (see below for details).

5.5 | Antecedent hypoglycemia

Moderate or sustained levels of hypoglycemia in the 24–48 h prior to exercise appear to blunt the counter-regulatory responses to exercise and may increase the risk for exercise-induced hypoglycemia.[78] Obesity and exercise in the cold may also blunt some of the counter-regulatory hormones (i.e., growth hormone, catecholamines)[79,80] which may increase hypoglycemia risk.

5.6 | Glycemia, musculoskeletal health, and exercise performance

An acute episode of mild to moderate hyperglycemia does not appear to impact exercise or sport performance in T1D.[7] However, even mild hypoglycemia negatively impacts reaction time and overall sport performance.[81] On the other hand, sustained hyperglycemia (days and weeks) likely impacts several metabolic and circulatory processes that could, at least in theory, negatively impact exercise capacity, including an apparent loss of muscle mass and muscle mitochondrial content, reduced muscle capillarization, and general dehydration.[82] In the long term, elevated HbA1c levels in youth with T1D may impact growth and development[83] and likely adversely affect musculoskeletal health.[84] For youth with diabetes, doing regular PA, prolonged periods of hyperglycemia caused by exercise, or the fear of developing hypoglycemia from exercise may negatively influence achieving overall glycemic management targets. Nonetheless, similar to youth with T2D,[17,77] days with increased PA may improve the likelihood of achieving glycemic targets in youth with T1D compared to days with inactivity.[85] There are currently no data on exercise performance and glycemia in youth with T2D.

6 | NUTRITION AND EXERCISE

6.1 | Nutrition requirements and food quality

Advice on sports nutrition to maximize performance will include information about the type and amount of food and the intake timing. The amount of carbohydrates and protein required at meals will vary with age, sex, and activity levels. For youth undertaking daily activities associated with health (i.e., 60 min of moderate to vigorous PA daily), daily food intake should be sufficient to meet the demands of the activity, provided meals are distributed regularly across the day. Country-specific guidelines on energy and macronutrient intake exist in many parts of the world and, in general, increased activity levels are linked to increased energy requirements. Calculating increased energy and carbohydrate requirements may be necessary for very active youth, and youth specific PA compendium tables offer comprehensive lists to aid energy expenditure calculations.[86] Advice on supplementary carbohydrates for hypoglycemia prevention should aim not to increase total energy intake above expenditure, and the use of snacks should not decrease dietary quality. The nutrition table (Table E)

suggests the most effective carbohydrate choices for hypoglycemia prevention with the lowest total energy content. Adequate fluid intake is essential to reduce the risk of dehydration.[87] In most situations, water or sugar-free fluids are most suitable for maintaining hydration. Detailed nutrition recommendations for health and exercise can be found in the ISPAD 2022 Consensus guidelines Chapter 10 for Nutritional Management in Children and Adolescents with Diabetes, along with further advice about nutritional supplements.

6.2 | Nutritional and sports supplements

There is minimal evidence on using protein or other nutritional supplements to support athletic performance in adolescents. Protein supplements in adolescent athletes may not have additional benefits for exercise performance[88] although there is some evidence they may reduce post-exercise inflammatory responses[88] and have acute benefits on post-exercise muscle anabolism; however, demonstrable muscle damage and recovery changes have not been clearly shown.[89] Therefore, protein supplementation should not be routinely recommended for youth partaking in regular PA.

Adolescent sports competitors often use sports supplements.[90,91] However, the International Society of Sports Nutrition's review of performance-enhancing supplements identified a dearth of efficacy data for their use in children under 18 years.[92] Therefore, counseling on using food to maximize training adaptions should be prioritized. Advice on the risks of sports supplement use, which include contamination with banned performance-enhancing substances, should be provided with guidance on anti-doping according to the sport and level of competition. Some sports begin anti-doping procedures below the age of 18 years. Educational programs on anti-doping in sports are available through many national sporting organizations. Information about therapeutic use exemption for insulin is available on the world anti-doping authority website (https://www.wada-ama.org).

6.3 | Alcohol

Adolescents and young adults need to understand the effects of alcohol on the response to exercise and falling BGLs. As some sports are associated with a "drinking" culture, alcohol safety advice should be provided without endorsing its consumption. Based on studies in adults with diabetes, alcohol impairs glucose counter-regulation by inhibiting hepatic gluconeogenesis (but not glycogenolysis) and increases the risk of hypoglycemia.[93–96] Alcohol should be avoided before and during exercise as it may increase hypoglycemia risk, including nocturnal hypoglycemia after exercise, and impair performance. If alcohol is consumed after exercise, it may be necessary to advise more aggressive insulin reductions and higher supplementary carbohydrate amounts from the adjustment tables discussed later in this chapter (Tables A–E).

6.4 | Low carbohydrate diets

No studies have specifically examined exercise performance of youth with diabetes using low carbohydrate diets. A recent systematic review of adult recreational exercisers without diabetes showed no impairment in aerobic performance or time to exhaustion after diet acclimatization on a low carbohydrate diet.[97] The only difference was higher FFA utilization.[97] However, a clinical trial has shown an impairment in exercise economy and performance when elite endurance athletes consumed a low carbohydrate diet.[98] The elite-level performance deficit has recently been replicated, and the impairment was attributed to blunted carbohydrate oxidation rates.[98]

It is questionable how relevant this research is for children with T1D who are administering exogenous insulin. People with T1D have peripheral circulating insulin levels that are 2.5 times higher than people without diabetes.[99] A high level of peripheral insulin alters hepatic and muscle metabolism.[100] In the absence of clinical trials, it is advisable to counsel against this dietary approach, especially for optimal exercise performance. If a child or family insists on a low carbohydrate diet, it is essential to provide advice on exercising safely. Following the insulin adjustment strategies suggested in Tables 2 and 3 are sensible to start. However, the amount of supplementary carbohydrates required during exercise may be less than indicated in Tables 4 and 5. An individualized assessment and process of trial and error with an evolving plan will be required.

6.5 | Elite athletes and high performers

Specific recommendations regarding increased nutritional requirements and advanced insulin adjustment strategies required to support high-performing athletes with diabetes are beyond the scope of this chapter. Youth who participate in elite-level sports should be referred to a team with multidisciplinary expertise in exercise and T1D management.

The nutrition section discusses calculating energy, carbohydrate, and protein requirements based on the regular training and competition schedule. A recent review article discusses bespoke insulin adjustments strategies and how to plan for dynamic training protocols for different modalities and exercise duration.[9,101–105]

7 | INTEGRATING INSULIN AND NUTRITION STRATEGIES FOR ACUTE EXERCISE MANAGEMENT

Tables 2–6 are included to illustrate the recommendations below along with clarifications regarding age and gender of study participants.

7.1 | Planned exercise

Planned exercise lasting at least 30 min requires therapy management strategies before, during, after, and then overnight. A wide range of insulin adjustment and nutrition strategies can be combined to keep the

TABLE 2 Insulin pump insulin adjustments and nutrition recommendations for before, immediately after, and overnight for aerobic, mixed, and anaerobic activity lasting at least 30 min.

		Before exercise		After exercise		
		Prandial insulin	Basal rate for non-fasting exercise	Post-exercise prandial insulin	Choose one or both options if exercise after 16:00 and exercise duration more than 30 min	
Exercise type	Plan execution	If meal is consumed more than 2 h before exercise, administer regular prandial dose to prevent hyperglycemia[108] If meal is consumed within 2 h of exercise, adjust prandial dose using these suggestions[107,109,110]	If exercise is more than 120 min since prandial insulin, basal reduction 90 min before[112]	Prandial insulin reduction	Basal rate change	If glucose level less than 10.0 mmol/L (180 mg/dl) low glycemic index carbs snack without bolus insulin before bed[128] If glucose level less than 7.0 mmol/L (126 mg/dl) add an additional 15 g protein[128]
Aerobic	>15.0 mmol/L (270 mg/dl) using starting plan	−25%[108,109]	−25%	−25%	Regular dose	0.2 g/kg/BW
	Starting plan	−50%[107–109]	−50%[112]	−50%[110]	−20% for 6 h[62]	0.4 g/kg/BW[107,110]
	<5.0 mmol/L (90 mg/dl) using starting plan	−75%[108,110]	−80%[112]	−75%	−40% for 6 h	0.6 g/kg/BW
Mixed	>15.0 mmol/L (270 mg/dl) using starting plan	−25%[108]	Regular dose	Regular dose[107,108]	Regular dose	0.2 g/kg/BW
	Starting plan	−50%[107,108]	−25%	−25%	−20% for 6 h	0.4 g/kg/BW[107]
	<5.0 mmol/L (90 mg/dl) using starting plan	−75%[108]	−50%	−50%	−40% for 6 h	0.6 g/kg/BW
Anaerobic	>15.0 mmol/L (270 mg/dl) using starting plan	Regular dose	Regular dose and small bolus 15 min pre-exercise	Regular dose[108]	Regular dose	0.2 g/kg/BW
	Starting plan	−25%[108]	Regular dose	−25%	−20% for 6 h	0.4 g/kg/BW
	<5.0 mmol/L (90 mg/dl) using starting plan	−50%[108]	−25%	−50%	−40% for 6 h	0.6 g/kg/BW

Note: BW, body weight. If body mass index centile is ≥91st then use the IBW in kg = (BMI at the 50th centile for age × [height in meter]^2),[111] unless the high BMI centile is due to large muscle mass. Consider reducing carbohydrate suggestions for populations with less lean body mass than healthy male adults, such as females and sedentary males. Adult male data.[108–110] Adult male and female data.[107,112,128] Pediatric male and female data.[62,111] The table suggests a starting plan (first recommendation to be given) that can then be personally adapted based (evidence level D.) The table provides guidance on how to adapt plans (first recommendation given in gray) based on trialing the starting plan. Only the before or after strategy that results in hyper- or hypoglycemia requires adjustment, not the whole plan.

TABLE 3 Multiple daily injections insulin adjustments and nutrition recommendations for before, immediately after, and overnight for aerobic, mixed, and anaerobic activity lasting at least 30 min.

		Before exercise	After exercise		
		Mealtime insulin	Post-exercise meal insulin	Choose one or both options if exercise after 16:00 and exercise duration more than 30 min	
Exercise type	Plan execution	If meal is consumed more than 2 h before exercise, administer regular prandial dose to prevent hyperglycemia[108] If meal is consumed within 2 h of exercise, adjust prandial dose using these suggestions[109,110]	Meal insulin reduction	Evening basal insulin	If glucose level less than 10.0 mmol/L (180 mg/dl) low glycemic index carbs snack without bolus insulin before bed[128] If glucose level less than 7.0 mmol/L (126 mg/dl) add an additional 15 g protein[128]
Aerobic	>15.0 mmol/L (270 mg/dl) using starting plan	−25%[109]	−25%	Regular dose[110]	0.2 g/kg/BW
	Starting plan	−50%[107–109]	−50%[110]	−20%[110]	0.4 g/kg/BW[107,110]
	<5.0 mmol/L (90 mg/dl) using starting plan	−75%[108,110]	−75%	−40%	0.6 g/kg/BW
Mixed	>15.0 mmol/L (270 mg/dl) using starting plan	−25%[108]	Regular dose[107,108]	Regular dose	0.2 g/kg/BW
	Starting plan	−50%[107,108]	−25%	−20%	0.4 g/kg/BW[107]
	<5.0 mmol/L (90 mg/dl) using starting plan	−75%[108]	−50%	−40%	0.6 g/kg/BW
Anaerobic	>15.0 mmol/L (270 mg/dl) using starting plan	Regular dose	Regular dose[108]	Regular dose	0.2 g/kg/BW
	Starting plan	−25%[108]	−25%	−20%	0.4 g/kg/BW
	<5.0 mmol/L (90 mg/dl) using starting plan	−50%[108]	−50%	−40%	0.6 g/kg/BW

Note: BW, body weight. If body mass index centile is ≥91st then use IBW in kg = (BMI at the 50th percentile for age × [height in meter]^2),[111] unless the high BMI centile is due to large muscle mass. Consider reducing carbohydrate suggestions for populations with less lean body mass such as sedentary individuals. Adult male data.[108–110] Adult male and female data.[107,128] Pediatric male and female data.[111] The table suggests a starting plan (first recommendation to be given) based evidence level D. These guidelines serve as starting point that require personalized adaptation. The table provides guidance on how to adapt plans (first recommendation given in gray) based on trailing the starting plan. Only the before or after strategy that results in hyper- or hypoglycemia requires adjustment, not the whole plan.

glucose level during activity in an exercise range of 5.0–15.0 mmol/L or 90–270 mg/dl and prevent exercise induced-hypoglycemia. It is paramount that the health care professional ensures the individual with diabetes, and if required, their family is aware that trial and error might be required and that plans must be adapted based on observed results. The insulin pump or continuous subcutaneous insulin infusion (CSII - Table 2) and multiple daily injections (MDI - Table 3) adjustment tables offer starting plans and adjustment protocols. Tables 4 and 5 offer guidance on how to calculate carbohydrates to prevent hypoglycemia just before and every 30 and 20 min during exercise, for people using SMBG and CGM, respectively. Ideas for meals, snacks, and carbohydrates during exercise can be found in Table 6.

Recommendations in Tables 2–6 are based on studies with small numbers of mainly healthy adults performed on treadmills or cycle ergometers and do not mimic real-world exercise for youths. Therefore, extrapolating to populations with lower lean body mass, such as youths who are sedentary, overweight, or obese, may be problematic. Specific considerations for these populations are discussed in the relevant sections and in the tables. Finally, using the tables will not produce consistent results across a population due to the considerable inter and intra-individual variation in glucose responses to the same exercise. The recipients of plans devised from the tables must be informed of their limitations and that they are merely a starting point requiring adaptation from trial and error.

TABLE 4 Glucose targets for fingerstick blood glucose devices and carbohydrate requirements for children and adolescents with T1D before and every 30 min during exercise, based on evidence level D.

	Expected glucose response during exercise based on the type of exercise, insulin on board and bolus adjustments, basal adjustments, and previous glucose control	
Sensor or blood glucose level	**Expected to fall during exercise**	**Expected to stay stable or rise during exercise**
Higher than 15.0 mmol/L (270 mg/dl) and ketones more than 0.6 mmol/L	Ketones >1.5 mmol/L: Follow usual ketone advice and avoid exercise Ketones 1.1–1.4 mmol/L: Give ½ correction dose by pen and wait 60 min to reassess Ketones 0.6–1.0 mmol/L: Give ½ correction dose by pen and wait 15 min to exercise	
Higher than 15.0 mmol/L (270 mg/dl) and ketones less than 0.6 mmol/L	Consider ½ of usual bolus insulin correction	
10.1–15.0 mmol/L (181–270 mg/dl)	No carbohydrate	
	Carbohydrate requirements (g/kg/BW/30 min do not exceed 60 kg)[b]	
Exercise target[a] 7.0–10.0 mmol/L (126–180 mg/dl)	0.2–0.5[117]	0
5.0–6.9 mmol/L (90–125 mg/dl)	0.5[101]	0.2[116]
Delay or stop exercise for 20 min 4.0–4.9 mmol/L (70–89 mg/dl)	0.3[190]	0.3[190]
3.0–3.9 mmol/L (54–70 mg/dl)	Treat hypoglycemia and delay exercise until greater than 4.9 mmol/L (89 mg/dl)	
Less than 3.0 mmol/L (54 mg/dl)	Treat hypoglycemia and do not start exercise due to impaired counter-regulatory hormone response	

[a]If risk of hypoglycemia or hypoglycemia unawareness is medium or high, increase exercise target level to 8.0–11.0 mmol/L (145–198 mg/dl) or 9.0–12.0 mmol/L (162–216 mg/dl) respectively.
[b]Do not exceed 60 kg when calculating carbohydrate amounts to prevent suggestions greater than the peak exogenous carbohydrate utilization of 1.0–1.2 g/min.[102–104,191] Also, if body mass index (BMI) percentile is ≥91st then use the body weight (BW) in kg = (BMI at the 50th percentile for age × [height in meter]^2),[111] unless the high BMI percentile is due to large muscle mass. Adult male data.[102–104,191] Adult male and female data.[116,117] Pediatric male data.[101] Pediatric male and female data.[111,190]

7.2 | Prior to planned exercise: Insulin adjustments and nutrition strategies

Exercise following an unadjusted mealtime insulin bolus may lead to hypoglycemia in youth with T1D[65,101] even when provided 15 g carbohydrate during exercise.[106] Reductions of pre-exercise prandial insulin by 25%–75% have proven successful for adults in preventing hypoglycemia for aerobic,[107–109] mixed,[108] and anaerobic[108] exercise. For adult males, prandial insulin reductions made 1–2 h before exercise[109,110] limit pre-exercise hyperglycemia when compared to reductions made 2–4 h before exercise.[108,110] When extrapolating the male adult data to youths, it seems important to ascertain the time gap between the meal and activity and counsel to aim to keep it ideally within 90 min when reducing bolus insulin before exercise. To prevent gastro-intestinal distress in adult males, a low-fat carbohydrate rich meal of 1.0–1.5 g/kg/BW has proven effective and is tolerated when eaten within 2 h of starting exercise.[109,110] If the young person has a body mass index (BMI) centile ≥91st, use their ideal body weight (IBW), unless the high BMI centile is due to large muscle mass. The BMI method for calculating IBW in kg (BMI at the 50th centile for age × [height in meters]^2) has been validated in pediatrics.[111]

When exercise is planned to begin more than 2 h after the meal, it is advisable to administer the regular meal insulin dose to prevent excessive hyperglycemia, which has been observed when reductions are made 2–4 h before exercise in adult males.[108] Insulin pump basal rate reductions of 50% and 80%, reduced the risk of hypoglycemia during aerobic exercise in the absence of prandial insulin when the reductions were activated 90 min before exercise.[112] However, disconnecting an insulin pump at the start of exercise generally does not prevent hypoglycemia during exercise[112,113] If the pre-exercise meal is to be consumed 2–3 h before exercise, keeping meal carbohydrate content to a maximum of 2 g/kg/BW, will prevent excessive circulating insulin at the start of exercise. Creating a gap of at least 3 h between mealtime and exercise is preferable to minimize circulating bolus insulin[114] and provide ample time for carbohydrates to be digested and assimilated for use during exercise.[115] If the gap is more than 3 h, a meal containing 1–3 g/kg/body weight (BW) of carbohydrate that is moderate to low in fat is recommended to improve liver and muscle glycogen stores.[115] Endurance athletes with high training loads may need 4 g/kg/BW.

TABLE 5 Glucose targets for CGM and carbohydrate requirements based on glucose value and trend arrows for children and adolescents with T1D before and every 20 min during exercise, based on evidence level D.[10]

		Expected glucose response during exercise based on the type of exercise, insulin on board and bolus adjustments, basal adjustments, and previous glucose control (If checking frequency is more than 20 min, select the carbohydrate amount based on a stable trend arrow and adjust according to checking frequency)	
Sensor or blood glucose level	**Trend arrow**	**Expected to fall during exercise**	**Expected to stay stable or rise during exercise**
Higher than 15.0 mmol/L (270 mg/dl) and ketones more than 0.6 mmol/L	All	Ketones >1.5 mmol/L: Follow usual ketone advice and avoid exercise Ketones 1.1–1.4 mmol/L: Give ½ correction dose by pen and wait 60 min to reassess Ketones 0.6–1.0 mmol/L: Give ½ correction dose by pen and wait 15 min to exercise	
Higher than 15.0 mmol/L (270 mg/dl) and ketones less than 0.6 mmol/L	→ ↗↑	Consider ½ of usual bolus insulin correction	
	↘↓	No carbohydrate	
		Carbohydrate requirements (g/kg/BW/20 min do not exceed 60 kg)[b]	
10.1–15.0 mmol/L (181–270 mg/dl)	↑	0	0
	↗	0	0
	→	0	0
	↘	0.1	0
	↓	0.2	0
Exercise target[a] 7.0–10.0 mmol/L (126–180 mg/dl)	↑	0	0
	↗	0.1	0
	→	0.2	0
	↘	0.3	0.1
	↓	0.4	0.2
5.0–6.9 mmol/L (90–125 mg/dl)	↑	0.1	0
	↗	0.2	0.1
	→	0.3	0.2
	↘	0.4	0.3
	↓[c]	0.5	0.4
4.0–4.9 mmol/L (70–89 mg/dl)	↑	0.2	0.1
	↗	0.3	0.2
Delay or stop exercise 20 min 4.0–4.9 mmol/L (70–89 mg/dl)	→	0.3	0.3
	↘[c]	0.4	0.4
	↓[c]	0.5	0.5
3.0–3.9 mmol/L (54–70 mg/dl)	All Arrows	Treat hypoglycemia and delay exercise until greater than 4.9 mmol/L (89 mg/dl)	
Less than 3.0 mmol/L (54 mg/dl)	All Arrows	Treat hypoglycemia and do not start exercise due to impaired counter-regulatory hormone response	

[a]If risk of hypoglycemia or hypoglycemia unawareness is medium or high, increase exercise target level to 8.0–11.0 mmol/L (145–198 mg/dl) or 9.0–12.0 mmol/L (162–216 mg/dl) respectively.
[b]Do not exceed 60 kg when calculating carbohydrate amounts to prevent suggestions greater than the peak exogenous carbohydrate utilization of 1.0–1.2 g per min.[102–104,191] Also, if body mass index (BMI) percentile is ≥91st then use the body weight (BW) in kg = (BMI at the 50th percentile for age × [height in meter]^2),[111] unless the high BMI percentile is due to large muscle mass.
[c]Consider blood glucose test as CGM value maybe lagging. Adult male data.[102–104,191] Pediatric male and female data.[111]

7.3 | During the planned activity: Insulin adjustments and nutrition strategies

The mainstay of glucose management during activity is the consumption of extra carbohydrates. Research shows 0.5–1.0 g/kg/h is required in the presence of high circulating bolus insulin,[101] but only 0.3–0.5 g/kg/h if more than 2 h have passed since the last prandial insulin.[116,117] The carbohydrate requirement table for people using SMBG offers starting suggestions for carbohydrates before and every 30 min during exercise (Table 4 and Appendix [Table A1] for weight banded suggestions). The suggestions are based on the exerciser's glucose level and weight and if the glucose level is expected to fall or

TABLE 6 Nutrition examples for before, during immediately after, and overnight for aerobic, mixed, and anaerobic activity lasting at least 30 min, based on level D evidence.

Before exercise	During exercise	Post-exercise	Before bed
Aim for a meal at least 180 min prior to exercise to minimizing circulating insulin[114] and maximize glycogen stores[115] following the post-exercise meal content and examples If eating within 180 min of exercise, aim to eat within 60–90 min of exercise to reduce the risk of pre-exercise hyperglycemia[109,110]	High glycemic index carbohydrate choices when testing frequently during exercise Medium glycemic index carbohydrate choices when testing infrequently or never during exercise	Meal within 90 min of completing exercise Prioritize including a protein source	Exercise post-16:00 and duration ≥30 min Glucose level < 10 mmol/L (180 mg/dl)[b]: Carb[128] Glucose level <7 mmol/L (126 mg/dl)[b]: Carb + protein[128]
Meal content within 60–90 min of exercise: Carb: 1–1.5 g/kg/BW, Protein: low, Fat: low[109,110]	*Carbohydrate amount*: Carbohydrate requirement table C and D	*Meal content*: Carb 1–4 g/kg/BW, Protein: ≥15 g, Fat: Moderate[115]	*Snack content*: Carb: 0.4 g/kg/BW low-medium glycemic index[107,110] Protein: 15 g
Breakfast examples for meal within 60–90 min[a]: Fruit salad Toast/marmite or vegemite/fruit Breakfast cereal/milk Oat based muesli bar Pikelets Bagel/low fat cream cheese Pancakes	*Fluid options*[a]: *Glucose based (most effective) options*: Isotonic sports drinks 6%–8% (6–8 g/100 ml) Glucose energy drinks 8%–10% (8–10 g/100 ml) Glucose shots 25% (25 g/100 ml) Glucose sports gels 60%–70% (60–70 g/100 ml) *Sucrose (glucose/fructose) options*: Fruit juice 11% (11 g/100 ml) Sweetened drinks 8%–10% (8–10 g/100 ml)	*Breakfast examples*[a]: Fruit salad/milk/nuts/yoghurt Toast/eggs/tomato/fruit Breakfast cereal/milk Rolled oats/milk/nuts/fruit Toast/Avocado/eggs Pancakes/bacon/mushrooms/tomato Omelette/cheese/salad/bread roll Crepes/chicken/pea salad	*Low-medium glycemic index carb options*[a]: 200 g milk (10 g) 1 slice multigrain bread or toast (15 g) 50 g cooked chickpeas (15 g) 1 large apple or medium banana (15 g) 200 g plain yoghurt (14 g) 50 g cooked rice (15 g) 30 g wholegrain breakfast cereal (15-20 g) 50 g cooked noodles or pasta (15 g)
Lunch examples for meal within 60–90 min[a]: Sandwich or bread roll/salad Rice cakes/vegemite or marmite Wrap/lean meat/salad Wheat biscuits/fruit Rice/stir-fry vegetables Toast/marmite or vegemite/fruit	*Solid options*[a]: *Glucose based (most effective) options*: Dextrose tablets (3 g each) Glucose tablets (4 g each) *Sucrose (glucose/fructose) options*: Candy/sweets 75%–90% (75–90 g/100 g)	*Lunch examples*[a]: Sandwich or bread roll/lean meat or cheese/salad Wholegrain toast/peanut butter/banana Wrap/chicken/salad/baked beans Wheat biscuits/low fat cottage cheese/fruit Cous Cous/hummus/vegetables/fruit Pasta/avocado/chicken/vegetables/pesto Quesadillas/vegetables/cheese	*Protein options*[a]: 50 g mixed chopped nuts (8 g) 2 eggs (14 g) 70 g canned fish (15 g) 150 g low fat cheese (15 g) 200 ml milk (7 g) 200 g plain yoghurt (7 g) 50 g hard cheese (12 g) 50 g cooked chickpeas (3 g)
Dinner examples for meal within 60–90 min[a]: Rice/vegetables/tomato-based sauce Vegetable soup/bread roll Tortilla/vegetables/salsa/guacamole/beans Jacket potato/baked beans Noodles/stir-fry vegetables	*If unable to monitor glucose level frequently or at all during exercise*[a]: Before or during exercise include: Banana (22 g/100 g) Breakfast bar (67 g/100 g) Muesli bar (53 g/100 g) Rice cakes (83 g/100 g) Up and Go (10 g/100 ml) Low fat natural yoghurt (7 g/100 g)	*Dinner examples*[a]: Pasta/tomato-based sauce/mincemeat/vegetables Rice/fish/vegetables/tomato-based sauce Pad Thai/meat or fish/salad Jacket potato/tuna/mayonnaise/salad Lasagna/garlic break/vegetables Nut or lentil-based curry/chapattis/salad Vegetable stew with beans/baked potato Mashed potato/lean sausages/vegetables	

[a]The examples are estimates that will vary by country, therefore, the reader must review the nutrition labels of individual products and adapt based on the carbohydrate per 100 ml or 100 g. BW, body weight. If BMI percentile is ≥91st then use BW in kg = (BMI at the 50th percentile for age × [height in meter]^2),[111] unless the high BMI percentile is due to large muscle mass, and use the lower end of carbohydrate ranges for sedentary individuals.
[b]Target glucose levels may be individualized. Adult male data.[109,110,114] Adult male and female data.[107,115,128] Pediatric male and female data.[111]

remain steady or rise during exercise. The expectation of glucose change during exercise should be based on exercise type, bolus insulin on board, changes to basal insulin, and previous exercise experience.

In individuals with diabetes using CGM systems, the glucose trends (direction of arrows) should be considered. The BGL should be measured if sensor glucose is borderline since sensor accuracy deteriorates with exercise. CGM can permit adjustment of carbohydrate amounts based on real-time glucose levels and trend arrows. Providing smaller amounts of supplementary carbohydrates every 10–20 min based on glucose level has been shown to eliminate clinically important hypoglycemia (<3.0 mmol/L or < 54 mg/dl). Table 5 (Appendix [Table A2] for weight banded suggestions) offers starting suggestions for carbohydrates to be consumed before exercise and then every 20 min based on glucose value and trend arrows in the recent ISPAD/EASD consensus statement.[10] For adequate interpretation of trend arrows in different CGM devices, it is important to understand their meaning (Table 7). To gain a deeper insight into CGM accuracy during exercise and how to mitigate issues, the reader is referred to the EASD/ISPAD consensus statement from which the summary of considerations is presented in Table 8.[10]

CGM lags by about 12 ± 11 min during prolonged aerobic exercise.[118] Therefore, it is recommended that individuals confirm glucose levels by capillary glucose measurements if impending or present hypoglycemia is noted.[118] Clinical trials of the benefits of CGM

TABLE 7 Explanation of commonly used CGM and isCGM devices with respect to trend arrows from the ISPAD/EASD consensus statement 2020.[10]

Device	Trend arrow	Interpretation within 15 min	Conforms with generic trend arrow as used in the position statement
Abbott devices Senseonics devices	↑	Increase >30 mg/dl (1.7 mmol/L)	↑
	↗	Increase 15–30 mg/dl (0.8–1.7 mmol/L)	↗
	→	Increase/decrease <15 mg/dl (0.8 mmol/L)	→
	↘	Decrease 15–30 mg/dl (0.8–1.7 mmol/L)	↘
	↓	Decrease >30 mg/dl (1.7 mmol/L)	↓
Dexcom devices	↑↑	Increase >45 mg/dl (2.5 mmol/L)	↑
	↑	Increase 30–45 mg/dl (1.7–2.5 mmol/L)	
	↗	Increase 15–30 mg/dl (0.8–1.7 mmol/L)	↗
	→	Increase/decrease <15 mg/dl (0.8 mmol/L)	→
	↘	Decrease 15–30 mg/dl (0.8–1.7 mmol/L)	↘
	↓	Decrease 30–45 mg/dl (1.7–2.5 mmol/L)	↓
	↓↓	Decrease >45 mg/dl (2.5 mmol/L)	
Medtronic devices[a]	↑↑↑	Increase >45 mg/dl (2.5 mmol/L)	↑
	↑↑	Increase 30–45 mg/dl (1.7–2.5 mmol/L)	
	↑	Increase 15–30 mg/dl (0.8–1.7 mmol/L)	↗
		Increase/decrease <15 mg/dl (0.8 mmol/L)	→
	↓	Decrease 15–30 mg/dl (0.8–1.7 mmol/L)	↘
	↓↓	Decrease 30–45 mg/dl (1.7–2.5 mmol/L)	↓
	↓↓↓	Decrease >45 mg/dl (2.5 mmol/L)	

[a]If Medtronic CGM system displays no trend arrow, this means that sensor glucose is stable as detailed below.

TABLE 8 Summary of isCGM and CGM use during exercise for T1D from the ISPAD/EASD consensus statement 2020.[10]

Accuracy
• Mean average relative difference (MARD) increases ~10% to 13.6% during exercise • Time lag between blood glucose and sensor glucose lengthens from ~5 min to 12–24 min • The faster the glucose is moving the greater the time lag between blood glucose and sensor glucose
Safety
• Set low alert higher than usual during exercise, for example, 5.6 mmol/L (100 mg/dl) • Change exercise target sensor glucose level based on exercise experience and risk of hypoglycemia • If sensor glucose drops lower than 3.0 mmol/L (54 mg/d) exercise should not be re-started • Use sensor glucose and trend arrow after exercise to determine if hypoglycemia prevention carbohydrate is required • Encourage followers where acceptable to support during and after exercise, and overnight • For systems without alerts and alarms encourage periodic checking overnight

technology on the SMBG and exercise behaviors for adolescents with T2D are needed.

The upper limit of gastrointestinal absorption of glucose is around 1.0 g/min in adult males.[102] By applying the male adult literature to youths, the carbohydrate calculations used for Tables 4 and 5 (appendices) were limited at 60 kg to prevent suggesting more glucose than can be absorbed to prevent delayed hyperglycemia. Rapidly absorbed high glycemic index products such as dextrose tablets, glucose drinks, and glucose gels will be the most effective when testing every 20 min (Table 5). Sports drinks with 8%–10% carbohydrates are effective during exercise in adolescents with T1D.[119] More slowly absorbed carbohydrates such as fruit, biscuits/cookies, chocolate, and sweets will likely increase the risk of hypoglycemia during exercise and hyperglycemia afterwards if consumed every 20 min. However, if testing is less frequent, more slowly absorbed carbohydrates such as fruit, cereal bars or low-fat biscuits may prevent initial hyperglycemia. Practical nutrition recommendations with meal suggestions for before, during and after exercise can be found in Table 6. Hyperglycemia can be rectified by administering half the usual correction dose if the glucose level is above 15.0 mmol/L (270 mg/dl) with ketones less than 1.5 mmol/L.[59]

7.4 | Immediately after planned activity: Insulin adjustments and nutrition strategies

Reductions of 50% in post-exercise prandial insulin have proven effective in preventing hypoglycemia in adult males after aerobic exercise.[110] However, glucose level post-exercise remains higher after mixed exercise when compared to aerobic,[107] suggesting smaller bolus reductions are needed after mixed and anaerobic exercise. In addition, in the 2 h after exercise muscle and liver glycogen replenishment and muscle protein synthesis rates are at their highest in adult males.[120] Therefore, extrapolating to youth, it seems prudent to take advantage of this anabolic window by recommending balanced meals after exercise with 1–4 g/kg/BW of carbohydrates and 15–20 g of protein.[107] Only endurance athletes will require 3 g/kg/BW or more of carbohydrates and IBW should be used if BMI centile ≥91st.

Completing short sprints just after the exercise finishes may help prevent hypoglycemia 120 min after exercise.[67] However, the practicality of completing all-out sprints may prove challenging after exercise. Therefore, this strategy may best be reserved for when not eating in the post-exercise window, where bolus reductions will prevent hypoglycemia.

The glucose level can rise sharply immediately after exercise and there are several potential reasons why this may occur.[59,121,122] Firstly, males undertaking exercise with many anaerobic components will build up both lactate and adrenaline in the bloodstream.[108] Lactate not cleared within exercising muscles is shuttled to the liver to be converted into glucose by the Cori cycle and returned to circulation. A high level of circulating adrenaline causes insulin resistance and the liver to release stored glycogen.[123,124] Completing a cool-down for 10–15 min may lower serum lactate levels and delivering a 50% reduced correction dose of insulin is a common suggestion.[59] However, cool-downs have not been tested experimentally and delivering 100% and 150% of correction insulin post-high intensity interval training were more effective than 50% and did not significantly increase rates of hypoglycemia.[125] If the exerciser disconnects the insulin pump for the activity, there will be inadequate circulating insulin once the exercise stops, leading to hyperglycemia.[126] One option is to bolus 50% of the missed basal rate before or during the activity. Finally, suppose the carbohydrate consumed during exercise exceeds 1.0 g/min and/or is a more slowly absorbed carbohydrates such as biscuits or chocolate. In that case, there will be a backlog of carbohydrates to be digested immediately after the exercise finishes without insulin present to cover. Consuming high glycemic options such as dextrose tablets, sports drinks, and gels in smaller amounts more frequently is the easiest way to avoid this cause of post-exercise hyperglycemia. Practical suggestions may be found in Table 6.

7.5 | Overnight following planned activity: Insulin adjustments and nutrition strategies

Following exercise lasting 45 min the risk of hypoglycemia lasts for 7–11 h, which increases the risk of overnight hypoglycemia for activity performed after 4 p.m.[61] Reducing background insulin by 20% for adults using MDI regimens has proven effective[110] and reducing basal rates for insulin pump users by 20% for 6 h overnight mitigates hypoglycemia in youth with T1D.[62] The efficacy of a 20% reduction has been corroborated in a closed-loop study where basal insulin was reduced on average 20% overnight following an exercise session.[127] If reducing insulin is not desired or practical, consuming a bedtime snack of 0.4 g/kg/BW of low to medium GI carbohydrate without bolus insulin has prevented hypoglycemia in adult males.[110]

TABLE 9 Exercise targets and settings for various hybrid closed-loop technology.

Device system	Sensor and pump technology	Standard glucose target	Exercise glucose target	Exercise TARGET Terminology	Additional information
MiniMed 670G/770G (Medtronic)	Guardian sensor 3 and 670G or 770G pump	6.7 mmol/L (120 mg/dl)	8.3 mmol/L (150 mg/dl)	Temp target	Program for duration of time, will automatically deactivate at end
MiniMed 780G (Medtronic)	Guardian sensor 3 and 780G pump	5.5 mmol/L (100 mg/dl) 6.1 mmol/L (110 mg/dl) 6.7 mmol/L (120 mg/dl)	8.3 mmol/L (150 mg/dl)	Temp target	Program for duration of time, will automatically deactivate at end
Control-IQ (Tandem)	Dexcom G6 sensor and Tandem t-slim X2 pump	6.2–8.9 mmol/L (112–160 mg/dl)	7.8–8.9 mmol/L (140–160 mg/dl)	Exercise activity Up to six personal profiles can be created with personalized basal doses, I:C, and ISF ratios for use with exercise mode	Manual start/stop – Cannot program a duration of time Exercise mode suspends insulin delivery at a higher predicted glucose than the standard mode. Overrides programmed sleep mode unless exercise mode switched off
CamAPS FX (CamDiab)[a]	Dexcom G6 sensor and Dana RS and Dana-i pump	5.8 mmol/L (105 mg/dl) (Customizable glucose target)	No set glucose value (Customizable)	Ease-off or Planned Ease-off	Program for duration of time, will automatically deactivate at end
Omnipod 5 (Insulet)[b]	Dexcom G6 sensor and Omnipod 5 Pod	6.1, 6.7, 7.2, 7.8, and 8.3 mmol/L (110, 120, 130, 140, 150 mg/dl) (Customizable glucose target)	8.3 mmol/L (150 mg/dl)	Activity feature	Enable for 1–24 h, will automatically deactivate at end
DIY APS (OpenAPS, AndroidAPS, Loop)	Variety of systems	Customizable	Set target as desired (Customizable)	Temporary target, profile switch, overrides, or activity mode	Program for duration of time or scheduled for specific time, will automatically deactivate at end

Abbreviations: APS, artificial pancreas system; DIY, do it yourself; I:C, insulin to carbohydrate ratio; ISF, insulin sensitivity factor.
[a]CamAPS has CE-marked approval in the European Union and United Kingdom and is currently only commercially available in Europe.
[b]Omnipod 5 received FDA approval and is only commercially available in the United States.

Additionally, a bedtime snack is only needed if the glucose level before bed is less than 10.0 mmol/L (180 mg/dl) and including 15 g of protein provided extra protection if the glucose is less than 7.0 mmol/L (126 mg/dl) in adult males.[128] Smaller snacks will almost certainly be needed for younger children, especially those with overweight or obesity. These before bed snack targets should be individualized based on glucose response and habitual activity levels.

Exercise for 45 min performed at midday does not have the same hypoglycemia-inducing effect overnight and therefore does not require the same adjustments.[129] This is important for school-aged children as it suggests that basal insulin dose adjustment is not required following daytime sports classes or lunchtime activities. The nutrition suggestions in Table 6 offer practical snack suggestions before bed.

7.6 | Twice-daily insulin regimens

For those using twice-daily insulin regimens that combine long- and short-acting insulin, adjusting mixed doses for exercise can be problematic, and the more straightforward strategy is to consume additional carbohydrates to prevent hypoglycemia. However, twice-daily insulin regimen is not recommended. Tables 4 and 5 offer supplementary carbohydrate suggestions for before and during exercise. Preventing hypoglycemia overnight after exercise lasting 30 min or more performed after 4 pm can be achieved by consuming an additional snack before bed based on the glucose level, (Tables 3 and 6).

7.7 | Unplanned exercise

Most activities for young children are unplanned, as they are sporadic in nature and usually last less than a minute.[130] These activities are managed as part of the usual daily routine. Unplanned opportunistic activities such as jumping on a trampoline or playing at school break (recess) time usually last less than 15 min and rarely cause hypoglycemia. However, if these activities last longer than 15 min, rapidly absorbed carbohydrates will likely be required. Confirming this, one study of 50 young people walking on a treadmill for four intervals of 15 min found a minimal glucose drop after 15 min. However, between 15 to 30 min half of the participants experienced a drop of more than 2 mmol/L (36 mg/dl).[106] Therefore, following the carbohydrate suggestions in Tables 4 and 5 for unplanned exercise lasting 20 min is recommended. These tables could also be used to manage gym lessons at school and activity camps. The suggestions should serve as a starting point that can be adapted based on experience.

The glucose-lowering effect of moderate-intensity exercise after eating has been established in a report combining four data sets (n = 120) that showed a mean glucose decrease of 4.2 mmol/L (76 mg/dl) after 45 min.[65] The most powerful predictor of glucose decrease was pre-exercise glucose level: subjects with a starting glucose level higher than 10.5 mmol/L (190 mg/dl) had a median (quartiles) drop of 6.1 mmol/L (4.3, 8.9) or 110 mg/dl (78, 160) with very few episodes of hypoglycemia.[65] This suggests using moderate activity to quickly treat hyperglycemia between meals may be a novel strategy worth exploring in clinical trials. In addition, for 100 youths, the implementation of the mnemonic "GAME," Glucose time in range desired, Alert on high set accordingly, Mode of moderate-intensity activity, Exercise on high alert between meals if possible for 10–40 min depending on glucose value and trend arrow, was the strongest predictor of time in range (3.9–10.0 mmol/L or 70–180 mg/dl) 6 months after attending structured education focused on pro-active CGM management.[131] A strategy like this may offer parents and children another option to improve time in range by quickly lowering between-meal hyperglycemia, provided the blood ketone level is not elevated. Using exercise in this way requires further research but holds potential for activity to improve time in range.

8 | HYBRID CLOSED LOOP STRATEGIES

8.1 | Single hormone (insulin-only) hybrid closed loop technology

Commercially available HCL availability varies worldwide. Each of the commercially available HCL systems has the option of activating an exercise or activity glucose target in anticipation of exercise or PA. The purpose of an "exercise target" is to increase glucose levels and maintain a higher BGL target during exercise by adjusting the insulin-delivery algorithm. Table 9 outlines some of the differences between commercially available device systems, including the various names used to describe an activity target (e.g., Temp target, Exercise activity, Ease-off) and the various glucose targets during exercise by device type.

8.2 | Exercise targets and pump suspension using hybrid closed loop technology

Longer duration (30+ minutes), low-to-moderate intensity aerobic exercise typically causes glucose levels to fall and increases the risk of hypoglycemia.[58] The following sections describe strategies to help reduce the risk of exercise-associated hypoglycemia for youth using HCL technology.

Irrespective of the HCL system being used, exercise targets optimally should be set well in advance of aerobic exercise. Similarly, studies have shown that using a HCL system, setting an exercise target 90–120 min before aerobic exercise (40+ min) also reduces the risk of hypoglycemia.[16,132] In situations where pre-planning for exercise is not possible, there is still value in setting an exercise target closer to the activity, even if the 90- to 120-min window is missed because setting an exercise target will stop the auto-correction bolus delivery (e.g., 770G/780G) and will increase the target glucose range so less basal insulin will be delivered during the activity.

For activities that may not cause drastic decreases in glycemia, (e.g., shorter duration activities [<30 min] and/or some high-intensity

anaerobic exercise), and fasted exercise, it may not be necessary to set an exercise target. However, Morrison et al.[132] recently showed that using the MiniMed® HCL system, setting an exercise target (i.e., temp target) 120 min before high-intensity exercise was effective in maintaining glucose time-in-range. For exercise of longer duration in youth the Tandem Control-IQ® system was compared with a remote monitored sensor-augmented pump system during a winter ski camp, showing improved percent time within range with the HCL system.[13] Further research is warranted to understand whether an exercise target is needed for various exercise intensities and durations.

Alternatively, some HCL users may choose to suspend insulin delivery (i.e., pump suspension) rather than set an exercise target to reduce the risk of hypoglycemia during aerobic exercise. For high-impact activities and certain contact sports (e.g., wrestling, martial arts, football, handball, etc.), pump suspension and/or pump disconnect may be preferred or even required. This may be a more effective strategy for shorter duration PA.[133] However, it is essential to turn off the HCL system, otherwise the algorithm will consider insulin delivered. Pump suspensions longer than 90 min should be avoided if not replaced by insulin administered for example every hour by connecting the pump or using an insulin pen for this purpose.

8.3 | Bolus adjustment strategies before and after exercise using hybrid closed loop technology

8.3.1 | Pre-exercise

Although there is limited research assessing the timing and specific bolus insulin adjustment strategies with HCL technology around exercise, this section was developed based on the existing, published literature[15] and expert opinion. Even with HCL technology, manual reductions in bolus insulin at the meal before exercise may be needed because meal bolus insulin action time may extend into the exercise session when the session is within 1–3 h of a meal. As is done for open loop CSII systems, persons using HCL systems should consider using a 25–75% bolus reduction for the meal preceding exercise. Using HCL technology, a recent study in adults by Tagougui et al.[15] found that the combination of an exercise target set just before exercise, along with a 33% reduction in mealtime bolus insulin, led to less hypoglycemia range (2.0 ± 6.2% time <3.9 mmol/L) as compared to an exercise target alone (7.0 ± 12.6%) or no announced exercise target with full bolus (13.0 ± 19.0%). Therefore, for aerobic and mixed exercise soon after a meal, we recommend a starting plan of 25% bolus reduction with the meal prior to exercise (Table 2). An important consideration is that not all commercially available systems have a specific function to allow for a bolus reduction. As such, one strategy is to enter fewer carbohydrates than what is being consumed into the HCL system. Some HCL systems (e.g., Tandem Control-IQ) allow multiple/additional profiles to be added to the pump. Using this approach, individuals may consider adding another "activity" profile with a higher insulin sensitivity factor (ISF) and less aggressive carbohydrate ratio (ICR). In turn, this will allow the HCL system to suggest a lower bolus insulin amount. However, there are currently no studies assessing these specific strategies and, therefore, they should be discussed with healthcare professionals, individualized, reviewed, and used with caution.

For higher-intensity anaerobic exercise or competition settings, a starting plan may include no bolus reduction (i.e., usual bolus dose) with the meal prior to exercise. It should also be noted that if the meal before exercise is high in carbohydrate content, a bolus insulin reduction may cause glycemia to rise before the onset of exercise, which will increase automatic basal insulin delivery on most HCL systems or even prompt automatic correction boluses right before exercise with the attendant increased hypoglycemia risk. This risk can be minimized by choosing a lower carbohydrate meal, where possible, and by setting the exercise target soon after the meal so that basal insulin delivery is curtailed to some degree.

8.3.2 | Post-exercise

Recommendations around bolus reductions with the meal post-exercise to reduce the risk of exercise-associated hypoglycemia are justified. As the guidance around bolus reductions post-exercise with HCL systems has not been well researched to date, thus suggestions in this section are based on expert opinion. The starting plan (see Table 2) for post-exercise meal insulin is a 25% bolus reduction, irrespective of the type of exercise.

8.4 | Carbohydrate needs before and during exercise using hybrid closed loop technology

There are a few important differences to guidance for carbohydrate intake for exercise for those on HCL systems. First, the timing of pre-exercise carbohydrate intake needs to be considered. Carbohydrate intake well before exercise (i.e., 20 min or more) tends to promote a rise in glycemia and subsequent increased insulin delivery by the HCL system. This may cause hypoglycemia during the activity. Second, the amount of carbohydrate consumed may need to be less than typical in settings where exercise mode has been activated well in advance of the activity and/or a pre-exercise bolus reduction has been made. The use of CGM systems informs decisions about carbohydrate intake to limit hypoglycemia during various forms of exercise based on the glucose concentration and directional trend arrows of the CGM.[10]

8.4.1 | Pre-exercise

Although consuming uncovered snacks 30 min before exercise can reduce hypoglycemia for males on MDI,[134] for HCL technology, the rise in sensor glucose levels associated with the uncovered snack will likely lead to a subsequent rise in automated insulin delivery and therefore increase the risk of hypoglycemia during the activity. The current consensus is that pre-exercise carbohydrate intake should be limited to within 5–10 min before the onset of exercise or if the

individual develops hypoglycemia prior to the exercise session. In situations when carbohydrate intake is necessary in the 1–2 h before exercise, an insulin bolus reduced by approximately 25% should be given (see above) and then the HCLsystem should be placed into "activity mode".

8.4.2 | During exercise

Individuals should use their CGM glucose and trend arrows (where applicable) to make decisions about carbohydrate intake needs to prevent hypoglycemia during exercise[10] (Table 5). During exercise, ingesting carbohydrates in smaller amounts may also reduce the likelihood of rebound hyperglycemia post-exercise. Additional strategies to reduce hypoglycemia include exercising with little-to-no bolus insulin in the circulation, if possible, or consider delaying exercise until the post-absorptive state (i.e., three or more hours after a meal with bolus insulin) to allow for prandial insulin levels to drop before exercise by placing the closed loop system into exercise mode. If hypoglycemia develops during exercise, individuals on closed loop systems may require less carbohydrate intake as a treatment (e.g., 10 g); however, this is also highly individualized based on the size of the individual and the amount of circulating insulin and counter-regulatory hormones.

Bolus reduction before exercise	• Consider a 25% bolus reduction with meal before exercise (otherwise glucose will rise and automated insulin delivery will increase before exercise, therefore insulin on board [IOB] will be higher) • Bolus reduction will also decrease total IOB at exercise onset
Exercise target before exercise	• Set 1–2 h before exercise • Resume at end of exercise • If increased risk of hypoglycemia, maintain higher exercise/activity target for 1–2 h in recovery
Bolus reduction and exercise target before exercise	• May consider 25% bolus reduction with meal before exercise and set exercise target 1–2 h before exercise
Lower IOB before exercise onset	• Consume main meal at least 3 h before exercise
Pump suspension or disconnect	• Avoid prolonged (>120 min) pump suspension – risk of hyperglycemia or increased ketones

8.5 | Post-exercise hyperglycemia

In most cases, HCL systems appear to manage mild post-exercise hyperglycemia well, particularly if the system is placed back into the standard (i.e., not activity) closed loop automated mode. In some cases, a small corrective insulin bolus (e.g., 50% of the usual correction dose) may be required in settings of extreme post-exercise hyperglycemia (i.e., >15.0 mmol/L, 270 mg/dl).

8.6 | Planned versus unplanned activity

Healthcare professionals should discuss various options of using HCL systems to prepare for exercise or PA based on the person's lifestyle and goals. For example, some youth may find pre-planning for exercise preferable whereas others may find pre-planning difficult and, therefore, choose alternate options for exercise. In the following section, we discuss the various HCL options for planned versus unplanned exercise to reduce the risk of exercise-associated dysglycemia.

8.7 | Planned exercise with hybrid closed loop technology

Based on limited clinical research on HCL strategies around exercise and expert consensus, the following options should be considered in situations where individuals have time to prepare for exercise:

8.8 | Unplanned exercise with hybrid closed loop technology

For situations where individuals do not have time to prepare for exercise, the following options may be considered:

Carbohydrate feeding before exercise	• Consider consuming carbohydrate snack 5–10 min pre-exercise • Carbohydrates too early pre-exercise will lead to glucose rise and automated insulin delivery • Smaller amount of carbohydrates may be needed for exercise because HCL technology can decrease automated insulin delivery if needed and deliver more insulin if needed
Carbohydrate feeding during exercise	• Consider carbohydrate feeding approximately every 30 min during activity
Bolus reduction after exercise	• If person is at increased risk of hypoglycemia or experiences hypoglycemia post-exercise, consider 25% bolus reduction with meal post-exercise as a starting point
Lower IOB before exercise onset	• Consume main meal at least 3 h before exercise
Pump suspension or disconnect	• Avoid prolonged (>120 min) pump suspension – risk of hyperglycemia or increased ketones

8.9 | Special considerations

In this section, particularly in situations where the above recommendations do not seem appropriate or effective, we highlight some special considerations and tricks around exercise. In addition, this section also aims to address some unique differences between HCL systems around exercise.

Switch to manual mode or open loop CSII to prepare for exercise	• Consider a 50%–80% basal reduction 90 min pre-exercise until end of exercise
Pump suspension or disconnect	• Avoid prolonged (>120 min) pump suspension – risk of hyperglycemia or increased ketones • Need to adjust only before exercise and then to prevent insulin deficiency during exercise by possibly adding at least 50% of the "usual basal" every hour
Tandem Control-IQ tricks for exercise	• Consider setting an "exercise activity" profile • To start an alternative and personalized "activity" profile 90 min before exercise with adjusted basal, I:C and ISF ratios • If minimal correction bolus of 0.05 U is delivered prior to activity, this will stop the possibility of an autocorrection from the system • Remember to deactivate the "exercise activity" profile to avoid postexercise hyperglycemia
CamAPS tricks for exercise	• Customize glucose target depending on previous experiences and use exercise mode • Use "Ease-Off" following possible hypoglycemia • Use "Boost" mode during prolonged hyperglycemia

9 | SPECIFICS FOR YOUTH WITH TYPE 1 DIABETES

9.1 | Glycemia and exercise performance

Among young people, it has been shown that only a few carry out planned adaptations before and during PA, which calls for the need for training and motivational talks.[135] Exercise-related acute hypoglycemia avoidance is an important goal for safety in youth with T1D; additionally, hypoglycemia impairs performance and may increase rate of perceived exertion. It remains uncertain, however, whether and to what degree acute hyperglycemia impairs exercise capacity. A recent study[7] of recreationally active adolescents and young adults with T1D comparing euglycemia with hyperglycemia in both normal and hypoinsulinemic states found that VO_2peak was only marginally lower when participants were clamped at 17.0 mmol/L (306 mg/dl) and peak sprint cycling power was, in fact, slightly higher. Reaction time was marginally impacted by hyperglycemia in the hypoinsulinemic state, but no other differences were found. Fuel utilization, VO_2 kinetics and other markers were not evaluated in this study. In adults,[136] with T1D, mild hyperglycemia (12.4 mmol/L; 223 mg/dl) did not impact exercise capacity or perceived exertion or carbohydrate oxidation.

Elevated HbA1c level is associated with impaired exercise capacity in adults with T1D,[137] but tight glycemia is associated with exercise capacity on par with those without T1D. Pulmonary, cardiac, and vascular responses to exercise are impaired in people with suboptimally controlled T1D, and chronic hyperglycemia in animal models attenuates beneficial effects of exercise training[138] with impaired aerobic remodeling of skeletal muscle. Thus, achieving long term target glycemic control is likely required for optimal cardiovascular fitness and exercise performance.

9.2 | Competition day

Acute hyperglycemia is commonly reported by youth with T1D around exercise or activities associated with competition, even when usually associated with euglycemia or hypoglycemia under training or low stress non-competitive conditions. An elevated adrenergic state likely contributes to increased hepatic glucose output and, possibly, insulin resistance. Given the paucity of clinical trials addressing this situation, a practical approach is favored emphasizing increased time to prepare for the planned competition, early glucose monitoring to detect emerging stress hyperglycemia and reducing the possibility of over-fueling prior to competition.

For those on insulin pump therapy, a temporary increase in basal insulin delivery can be set at the predicted (or observed) onset of hyperglycemia; however, it is important to reduce the rate back to baseline or below shortly before competition onset to avoid hypoglycemia resulting from resolution of the adrenergic state during or shortly after activity competition. For those using a HCL system, delaying the use of the exercise mode may reduce the risk of stress-related hyperglycemia, by allowing for increased basal insulin delivery and/or continuation of automatic correction doses.

Practicing a pre-match or pre-race routine may be beneficial for those who frequently experience competition-associated hyperglycemia. This may include performing a low intensity aerobic warmup (walk or light jog) to reduce counter-regulatory hormones and facilitate glucose uptake, or other mental preparedness strategies. Data are scarce on the effectiveness of these strategies. Acute excitement or stress-mediated hyperglycemia will likely settle quickly with the activity itself. The risk of delayed, or post-exercise hypoglycemia likely increases with aggressive correction of pre-competition excitement or nervousness-related hyperglycemia.

9.3 | Prolonged pump disconnection

Prolonged pump disconnection is sometimes desirable. Sports performed in water (swimming, diving) or on water (sailing) are reasons to disconnect some devices. Likewise, devices should be disconnected for some contact sports (e.g., wrestling, handball, ice hockey, American/Australian football). Sometimes the rationale for disconnecting the pump is to reduce the risk of hypoglycemia. For youth with T1D using insulin pump therapy, stopping the basal insulin infusion (i.e., pump suspension/disconnection) at the start of moderate aerobic exercise (around 60 min duration) in the late afternoon may reduce the risk of hypoglycemia during the exercise period.[139] However, pump suspension may not be as effective as reducing basal insulin[112] (or setting a higher exercise target) 90–120 min in advance of exercise. Although generally uncommon,[140] some concerns around prolonged pump suspension (>120 min) especially in younger children (4–9 years of age),[141] include the potential increase in blood ketone levels and the possibility of forgetting to resume insulin delivery post-exercise. If disconnection is used for more than 90 min, different strategies can be used to avoid insulin deficiency: reattach pump every 60 min and administer a bolus corresponding to approximately 50% of the standard insulin administration per hour or use a hybrid regimen of injected insulin described below.

9.4 | Environmental considerations: open water swimming/surfing/sailing, ambient temperature, high altitude, and scuba diving

9.4.1 | Open water swimming/surfing/sailing

Open water swimming, surfing, and sailing expose the body to both cold temperature (see below) and water. Prolonged pump disconnection may be required (see above) and/or insulin pump treatment combined with insulin pen treatment and selected insulin type to adapt to the length of time the pump is disconnected. A hybrid regimen of injected insulin degludec and insulin pump therapy (disconnected during exercise) has been shown to be safe as well as effective in adults.[142] The same approach with a combination of insulin pump treatment and injected insulin glargine in children also showed that this strategy is feasible and might reduce the risk of hyperglycemia and ketoacidosis during prolonged pump suspension.[143]

9.4.2 | Ambient temperature

High ambient temperature tends to increase the insulin absorption rate and low ambient temperature has the opposite effect.[144] The latter could have an impact during open water swimming (mentioned above), using a wetsuit can protect against the cold. High ambient temperature might also result in stress, resulting in greater energy expenditure, thus increasing the risk of rapidly decreasing glucose levels.

The accuracy of blood glucose meters can be affected by several factors, including temperature and altitude (see below), and it is recommended to acquire knowledge of which limit values apply to the meter of use. Moreover, high temperature might result in dehydration which also may affect the accuracy of CGM devices. Therefore, hydration is of utmost importance as severe dehydration may cause inaccurate sensor glucose readings.

Conversely, low temperatures also may reduce measurement accuracy or cause no glucose value to be obtained. This situation is quite typical for blood glucose monitors kept at temperatures below 0 degrees Celsius (32 degrees Fahrenheit). Thus, during PA in such circumstances CGM is a better option.[145]

9.4.3 | High altitude

Downhill skiing or rock climbing are examples of exercises at high altitude. High altitude-induced anorexia and increased energy expenditure might cause dysglycemia and hypoxia may cause erroneous decisions. Exercise and stress during these conditions also affects the counter-regulatory hormonal response. Thus, optimal glycemia becomes essential. As blood glucose meters may be inaccurate at high altitude; therefore, CGM could be recommended for combined use. Additional information about exercise in high altitude conditions can be found in a review.[146]

9.4.4 | Scuba diving

Formal guidelines on diving in people with insulin-treated diabetes was published in the early 1990 s. Subsequent consensus was then created following a workshop in 2005.[147]

Diving with concomitant insulin-treated diabetes is now approved with certain reservations in most countries around the world.[148,149] However, careful and periodic evaluation is still required to ensure that participation in diving activities is appropriate. In connection with diving, it is therefore important to have careful self-monitoring, well-thought-out adjustments to insulin doses and carbohydrate intake before each diving occasion.

Glucose levels should be checked at 60, 30, and 10 min before a dive and immediately after a dive. During this period, stable glycemia without falling values or trends is sought, and levels in the safe zone of 8.3 mmol/L (150 mg/dl) as a minimum before dive.[150]

Applicable to youth, programs are available to allow scuba diving at shallower depth limits, but in combination with diabetes other aspects must also be considered in addition to age. The individual who starts diving should generally be fit-to-dive but also have a suitable personality and well-controlled glycemia. Regarding youth, this also means that the individual must have the ability to make the right decision in urgent situations, including an ability to assess the consequences of decisions. With this as a basis, a Junior Open Water Diver Certificate can only be recommended in rare cases in youth with T1D, whereas the limiting factor in T2D in the same age group possibly is being fit-to-dive.

10 | CONTRAINDICATIONS TO EXERCISE AND SPORTS

T1D should not be a contraindication to participation in physical education and sport participation at each level of education, in training, and in competitions. The optimal target range for BGL before exercise is between 90 and 270 mg/dl (5.0–15 mmol/L). In persons with diabetes using CGM systems, the glucose trends should be considered. The BGL should be measured if sensor glucose is borderline since sensor accuracy deteriorates with exercise. Persons with diabetes with BGL in the optimal range can usually proceed safely with exercise, carbohydrate intake, and insulin dosing adjustments.

10.1 | Temporary contraindications to exercise

1. Episode of severe hypoglycemia within the previous 24 h (hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery). Antecedent severe hypoglycemia impairs the hormonal counter-regulatory response during exercise, thus increasing the risk for recurrent hypoglycemia.[151]
2. Hyperglycemia ≥270 mg/dl (15.0 mmol/L) with concomitant ketonemia/ketonuria due to insulin deficiency and not carbohydrate excess. Ketonemia ≥1.5 mmol/L is an absolute contraindication to initiation and continuation of physical exercise. In the case of ketonemia 1.0–1.4 mmol/L (urine ketones ++) exercise should be postponed until ketone levels normalize after administration of an insulin correction bolus.
3. Injury and acute infection. They may precipitate hyperglycemia in persons with diabetes because they tend to increase catecholamine and cortisol responses.

In addition to temporary contraindications to exercise, contraindications to competitive sport should be considered. Persons with diabetes with significantly unstable diabetes, frequent severe acute diabetic complications and advanced chronic complications of the disease should not participate in competitive sports until the disorder is stabilized.

11 | SCHOOLS AND CAMPS

Schools frequently provide opportunities for physical activity for many youth. The school environment has the potential to encourage physical activity in youth through physical education lessons, extracurricular activities (structured physical activity), and recess or lunchtime (discretionary physical activity). Students with diabetes should fully participate in physical education classes and other physical activities at school provided they do have any contraindications to exercise.

Physical education lessons and other active parts of the school day may be associated with glycemic disturbances. Good communication and cooperation between the student, their health care provider, parents, school nurse, physical education instructor or team coach, and goal setting that includes a well-designed regimen of glucose measurements, insulin adjustments and nutrition during and after exercise are essential. Therefore, education about diabetes is essential and virtual courses in diabetes are available (e.g., in Australia T1D Learning Centre - Courses).

For physical education lessons, a diabetes care plan should be developed, including detailed instructions for the students and their teachers and coaches. The main goal is to avoid hypoglycemia during and after exercise. For most physical activities at school, the guidelines are similar to those presented above.

Dedicated camps for children with T1D provide an excellent opportunity to learn additional skills to manage physical activity. Counseling on nutrition and insulin adjustment for exercise can lower HbA1c levels.[152] Children gain experience, which they can also share with others with diabetes. Furthermore, health care professionals can also benefit from such experiences.[153]

12 | EXERCISE IN CHILDREN WITH DIABETES ON INSULIN LIVING IN LIMITED CARE SETTINGS

Although intensive insulin regimen (MDI and CSII) is strongly recommended for the treatment of youth with T1D, substantial numbers of youth with T1D still use conventional insulin regimens.[154–156]

In many low-income countries, glucose test strips are not covered by universal health coverage. Even optimal SMBG (at least four times/day), is not possible due to the costs.[157] Even when blood ketone testing is available, the cost is high and not widely used by many persons with diabetes. For children using conventional insulin regimens together with limited SMBG, maintaining normoglycemia during exercise is challenging.

12.1 | Conventional insulin regimen

In conventional regimens, a combination of NPH and regular insulin or rapid-acting insulin analog are administered at breakfast and dinner time, or premixed insulin is administered twice daily. However, this type of regimen is not recommended.

When exercise occurs after meal, the dose of premixed insulin should be reduced by approximately 20%–50%[158] in order to reduce the risk of hypoglycemia during exercise, although hyperglycemia might occur later during the day because the amount of intermediate-acting insulin is decreased concomitantly.

If exercise occurs within 2–3 h after insulin injection and is planned, the dosage of rapid-acting insulin or regular insulin can be reduced. If the exercise will occur around the peak of NPH action (e.g., at noon) or exercise will last for hours, then the dose of NPH should be reduced. However, in many circumstances, even with the reduced dosage of insulin, individuals might still require extra carbohydrate intake during exercise. If exercise is unplanned, carbohydrate intake prior to and during exercise is recommended.

13 | TYPE 2 DIABETES AND EXERCISE

Much of the above part of the guidelines applies also to T2D and this section gives a few additional considerations to care of youth with T2D. Comorbidities are described in ISPAD 2022 Consensus guidelines Chapter 3 on Type 2 diabetes in children and adolescents.

13.1 | Physical activity improves cardiovascular health for adolescents with T2D

Daily PA is a cornerstone for preventing cardiometabolic complications associated with T2D and a clinical target in national and international guidelines for diabetes care.[1,159,160] Systematic reviews reveal robust dose–response associations between PA and several cardiometabolic health outcomes in healthy weight and obese youth.[161–163] These associations were replicated in experimental studies among adolescents living with obesity.[164–167] Importantly, the cardiometabolic health benefits associated with regular moderate to vigorous PA are evident in adolescents living with various forms of chronic disease.[168,169] There is a significantly smaller body of research on the role of PA for cardiometabolic health for adolescents with T2D.

Only three studies to date have examined the association between PA[17,77,170] and cardiometabolic health outcomes in adolescents with T2D, and all of them are cross-sectional. The largest study ($n = 588$) relied on surveys delivered during clinic visits and found that adolescents with T2D who report being active on three or more days per week display lower HbA1c levels and higher high density lipoprotein cholesterol, compared to less active adolescents.[77] A recent observational study from Canada found that that physically active adolescents with T2D were 40% less likely to have albuminuria (aOR: 0.60; 95% CI: 0.19, 0.84) and 50% less likely to have HbA1clevels above 8.0% (>60 mmol/mol; aOR: 0.50; 95% CI: 0.26, 0.98).[17] Adolescents with T2D who engaged in regular vigorous intensity activity also observed a trend towards lower odds of nocturnal hypertension (aOR: 0.54; 95% CI: 0.27, 1.07). Collectively, these observations provide some evidence that regular PA is associated with better cardiometabolic health in adolescents with T2D. RCTs, however, are needed to confirm these observations.

13.2 | Psychosocial factors are common and impede behavior change among adolescents with T2D

For many adolescents with T2D, implementing healthy lifestyle behaviors, including daily PA, is challenging.[171,172] This is due, in part, to exposure to psychosocial factors including adverse childhood experiences, poverty[173,174] and mental health disorders.[175–180] Mental health disorders are common among adolescents with T2D,[181,182] reducing quality of life and readiness to adopt regular daily PA.[46] For example, the odds of being ready to adopt new health behaviors (including daily PA) are ~14% lower for every unit increase in anxiety, depression, and emotional distress among adolescents with T2D.[46] In contrast, adolescents with T2D who reported having more resilient characteristics, particularly a connection to others and a sense of mastery over their lives, were 5%–10% more likely to be in the action and maintenance stage of change.[46] There is an urgent need to develop behavioral lifestyle interventions that specifically address these stressors and support adolescents with T2D to increase their daily PA.

13.3 | Conventional approaches to behavior change are ineffective for adolescents living with T2D

Changing behaviors among adolescents at risk for or living with T2D is challenging, and the optimal approach for increasing PA among adolescents with T2D remains uncertain. Recent systematic reviews[183–185] suggest that the efficacy of conventional behavioral lifestyle interventions for adolescents living with obesity is modest and rarely sustained. The modest effects may be related to the observation that ~80% of the RCTs of behavioral lifestyle interventions offered only 30 min of support weekly, and only 2 of 35 interventions addressed psychosocial factors.[186,187] The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was the only therapeutic trial that compared a behavioral lifestyle intervention that included increasing daily PA to standard of care for adolescents living with T2D.[188] This 2-year long intensive lifestyle intervention was grounded in the tenets of cognitive behavioral therapy (CBT) and provided extensive support for adolescents with T2D to lose weight and increase PA.[188] Despite rigorous efforts by the behavioral team, the intensive lifestyle intervention was not successful in maintaining target HbA1c levels (<8% [<60 mmol/mol])[48] or lifestyle behaviors.[189] Failure to address psychosocial factors was identified as a possible explanation for the poor efficacy of this approach.[189] RCTs are needed to determine the optimal approach to support adoption and maintenance of regular daily PA for adolescents living with T2D.

ACKNOWLEDGEMENTS

We are grateful for excellent revision including valuable comments from Jane Yardley, and guidance provided by Leena Priyambada.

CONFLICT OF INTEREST

Peter Adolfsson has received speaker's honoraria from Dexcom, Eli Lilly, Insulet, Novo Nordisk, Sanofi, and Tandem in the last 24 months. He has had consulting fees and/or advisory positions with Dexcom, Eli Lilly, Medtronic, Novo Nordisk, and Roche. Craig E. Taplin has received honoraria from Medtronic Diabetes Australia, Insulet Australia and Eli Lilly Australia. Dessi P. Zaharieva has received speaker's honoraria from Medtronic Diabetes, Ascensia Diabetes, and Insulet Canada; and research support from the Helmsley Charitable Trust and ISPAD-JDRF Research Fellowship. She is also on the Dexcom Advisory board. John Pemberton has worked for Medtronic from 2011 to 2016 and has attended two SIGMA CGM educational events sponsored by Dexcom in 2017 and 2019. Elizabeth A. Davis has received honoraria from Eli Lilly Australia in the last 24 months. Michael C. Riddell has received speaker's honoraria from Novo Nordisk, Eli Lilly, Dexcom and Roche

in the last 24 months. He has had consulting fees and/or advisory positions with Zealand Pharm, Zucara Therapeutics, Eli Lilly, and Indigo Diabetes. Jonathan McGavock: none. Othmar Moser has received speaker's honoraria from Medtronic, Sanofi, Novo Nordisk and TAD Pharma. Research funding/support: Novo Nordisk, Sanofi, Abbott, Medtronic, Dexcom, Maisels, Horizon 2020, EFSD. Agnieszka Szadkowska has received speaker's honoraria from Medtronic Diabetes, Ascensia Diabetes, Abbott, Dexcom, Roche Diabetes, NovoNordisk, Eli Lilly, Sanofi, has been a member of advisory board for Medtronic Diabetes, Ascensia Diabetes, Abbott, Dexcom, Roche Diabetes, NovoNordisk, Eli Lilly, and has received a research funding from Roche Diabetes. Prudence Lopez: none. Jeerunda Santiprabhob has received speaker's honoraria from Sanofi, Novo Nordisk, and Ferring and has been a member of Thailand advisory board of Liraglutide and Norditropin (Novo Nordisk). Elena Frattolin: none. Gavin Griffiths: none.

DATA AVAILABILITY STATEMENT

All authors conceived the guideline and discussed the content and the structure of the manuscript. All authors contributed to the manuscript and critically read and revised the manuscript including tables and figures.

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How to cite this article: Adolfsson P, Taplin CE, Zaharieva DP, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Exercise in children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(8):1341-1372. doi:10.1111/pedi.13452

APPENDIX A

TABLE A1 Glucose targets for fingerstick blood glucose devices and carbohydrate requirements for youth with T1D before and every 30 min during exercise, based on evidence level D.

	Expected glucose response during exercise based on the type of exercise, insulin on board and bolus adjustments, basal adjustments, and previous response to exercise (Carbohydrate per 30 min by body weight in kilograms[a])					
Sensor or blood glucose level	**Expected to fall during exercise**			**Expected to stay stable or rise during exercise**		
Higher than 15.0 mmol/L (270 mg/dl) and ketones more than 0.6 mmol/L	Ketones >1.5 mmol/L: Follow usual ketone advice and avoid exercise Ketones 1.1–1.4 mmol/L: Give ½ correction dose by pen and wait 60 min to reassess Ketones 0.6–1.0 mmol/L: Give ½ correction dose by pen and wait 15 min to exercise					
Higher than 15.0 mmol/L (270 mg/dl) and ketones less than 0.6 mmol/L	Consider ½ of usual bolus insulin correction					
10.1–15.0 mmol/L (181–270 mg/dl)	No carbohydrate					
Weight (kg)[b]	10–30 kg	30–50 kg	>50 kg	10–30 kg	30–50 kg	>50 kg
Exercise target[a] 7.0–10.0 mmol/L (126–180 mg/dl)	2–12 g[117]	6–25 g[117]	12–24 g[117]	0 g	0 g	0 g
5.0–6.9 mmol/L (90–125 mg/dl)	5–15 g[101]	15–25 g[101]	30 g[101]	2–6 g[116]	6–10 g[116]	12 g[116]
Delay or stop exercise for 20 min 4.0–4.9 mmol/L (70–89 mg/dl)	3–9 g[190]	9–15 g[190]	18 g[190]	3–9 g[190]	9–18 g[190]	18 g[190]
3.0–3.9 mmol/L (54–70 mg/dl)	Treat hypoglycemia and delay exercise until greater than 4.9 mmol/L (89 mg/dl)					
Less than 3.0 mmol/L (54 mg/dl)	Treat hypoglycemia and do not start exercise due to impaired counter-regulatory hormone response					

[a]If risk hypoglycemia or hypoglycemia unawareness is medium or high, increase exercise target level to 8.0–11.0 mmol/L (145–198 mg/dl) or 9.0–12.0 mmol/L (162–216 mg/dl), respectively.

[b]If body mass index (BMI) percentile is ≥91st then use body weight (BW) in kg = (BMI at the 50th percentile for age × [height in meter]^2),[111] unless the high BMI percentile is due to large muscle mass. Adult male data.[102–104,191] Adult male and female data.[116,117] Pediatric male data.[101] Pediatric male and female data.[111,190]

TABLE A2 Glucose targets for CGM and carbohydrate requirements based on glucose value and trend arrows for youth with T1D before and every 20 min during exercise, based on evidence level D.

Sensor or blood glucose level	Trend arrow	Expected glucose response during exercise based on the type of exercise, insulin on board and bolus adjustments, basal adjustments, and previous glucose control (If checking frequency more than 20 min, select the carbohydrate amount based on a stable trend arrow and adjust according to checking frequency)					
		Expected to fall during exercise			Expected to stay stable or rise during exercise		
Higher than 15.0 mmol/L (270 mg/dl) and ketones more than 0.6 mmol/L	All	Ketones >1.5 mmol/L: Follow usual ketone advice and avoid exercise Ketones 1.1–1.4 mmol/L: Give ½ correction dose by pen and wait 60 min to reassess Ketones 0.6–1.0 mmol/L: Give ½ correction dose by pen and wait 15 min to exercise					
Higher than 15.0 mmol/L (270 mg/dl) and ketones less than 0.6 mmol/L	→↗↑	Consider ½ of usual bolus insulin correction					
	↘↓	No carbohydrate					
Weight (kg)[b]		10–30 kg	30–50 kg	>50 kg	10–30 kg	30–50 kg	>50 kg
10.1–15.0 mmol/L (181–270 mg/dl)	↑						
	↗						
	→						
	↘	1–3 g	3–5 g	6 g			
	↓	2–6 g	6–10 g	12 g			
Exercise target[a] 7.0–10.0 mmol/L (126–180 mg/dl)	↑						
	↗	1–3 g	3–5 g	6 g			
	→	2–6 g	6–10 g	12 g			
	↘	3–9 g	9–15 g	18 g	2–6 g	6–10 g	12 g
	↓	4–12 g	12–20 g	24 g	3–9 g	9–15 g	18 g
5.0–6.9 mmol/L (90–125 mg/dl)	↑	1–3 g	3–5 g	6 g			
	↗	2–6 g	6–10 g	12 g	1–3 g	3–5 g	6 g
	→	3–9 g	9–15 g	18 g	2–6 g	6–10 g	18 g
	↘	4–12 g	12–20 g	24 g	3–9 g	12–20 g	18 g
	↓[c]	5–15 g	15–25 g	30 g	4–12 g	12–20 g	24 g
4.0–4.9 mmol/L (70–89 mg/dl)	↑	2–6 g	6–10 g	12 g	1–3 g	3–5 g	6 g
	↗	3–9 g	9–15 g	18 g	2–6 g	6–10 g	18 g
Delay or stop exercise 20 min 4.0–4.9 mmol/L (70–89 mg/dl)	→	3–9 g	9–15 g	18 g	3–9 g	9–15 g	18 g
	↘[c]	4–12 g	12–20 g	24 g	4–12 g	12–20 g	24 g
	↓[c]	5–15 g	15–25 g	30 g	5–15 g	15–25 g	30 g
3.0–3.9 mmol/L (54–70 mg/dl)	All Arrows	Treat hypoglycemia and delay exercise until greater than 4.9 mmol/L (89 mg/dl)					
Less than 3.0 mmol/L (54 mg/dl)	All Arrows	Treat hypoglycemia and do not start exercise due to impaired counter-regulatory hormone response					

[a]If risk hypoglycemia or hypoglycemia unawareness is medium or high, increase exercise target level to 8.0–11.0 mmol/L (145–198 mg/dl) or 9.0–12.0 mmol/L (162–216 mg/dl) respectively.

[b]If body mass index (BMI) percentile is ≥91st then use the body weight (BW) in kg = (BMI at the 50th percentile for age × [height in meter]^2),[111] unless the high BMI percentile is due to large muscle mass.

[c]Consider blood glucose test as CGM value maybe lagging. Pediatric male and female data.[111]

Received: 29 September 2022 | Accepted: 30 September 2022

DOI: 10.1111/pedi.13428

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Psychological care of children, adolescents and young adults with diabetes

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KEYWORDS: adolescents, children, diabetes, psychological care, type 1, type 2, young adults, youth

1 | WHAT IS NEW OR DIFFERENT

- Psychological care of youth with type 1 diabetes (T1D) as well as type 2 diabetes (T2D) is covered.
- Additional sections on the psychological assessment, communication, the health care team and psychological impact of technology are added
- Professionals with expertise in the mental health of children and adolescents are essential members of interdisciplinary diabetes health care team. **B**
- Mental health professionals should be available to interact with youth and their families, and also to support the diabetes team in the recognition and management of mental health and behavior problems. **C**
- It is preferable that mental health specialists who interact with children with diabetes have training in diabetes and its management. **E**

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | Collaborative care

- Psychosocial care should be integrated with collaborative, person-centered medical care and provided to all youth with diabetes and their families. **A**

2.2 | Integrating psychosocial assessments in routine diabetes care

- Age-appropriate and validated assessment tools should be routinely implemented in clinical practice to monitor and discuss

overall psychosocial well-being and quality of life (QoL) of all youth with diabetes. **A**
This should include the well-being of caregivers. **B**

- Screening for symptoms of depression, diabetes distress and disordered eating in children aged 12 and above using validated tools should be done at the initial visit, at periodic intervals and when there is a change in disease, treatment, or life circumstance. **B**
- Psychosocial problems should be addressed upon identification. If an intervention cannot be initiated during the visit when the problem is identified, a follow-up visit or referral to a mental health specialist should be scheduled during the visit. **B**
- Cognitive capacity and school functioning should be monitored especially in children with early onset of T1D (< age 7), as well as those who experience significant dysglycemia around the time of onset (evidenced by diabetic ketoacidosis [DKA], recurrent severe hypoglycemia, and/or severe hyperglycemia) **A**

2.3 | Diabetes management

- Routine assessment should be done for developmental adjustment to, and understanding of, diabetes management, including diabetes-related knowledge, insulin adjustment skills, goal setting, problem-solving abilities, and self-management autonomy and competence. This is especially important during late childhood and during adolescence. **B**
- When making treatment recommendations providers should consider the perceived treatment burden and self-efficacy, level of social and family support, and presence of significant mental health issues. **B**

2.4 | Diabetes in context

- The interdisciplinary team should assess general family functioning (stress, conflict, cohesion, adaptability, parental psychopathology), and diabetes-related functioning (communication, parental involvement and support, roles and responsibilities for self-management behaviors) especially during periods of transition (e.g., at diagnosis, at start of a new treatment plan, adolescence) and when there may be cultural or family based difficulties in adjustment to diabetes. **B**
Referral to mental health professional is recommended when necessary. **E**
- Adolescents should assume increasing responsibility for diabetes management tasks with continuing, mutually agreed, parental involvement and support. **B**
- Providers need to navigate the shift in responsibilities from parents to their children by being attuned to youth's evolving competencies and readiness for independent self-care, while also taking into account the need for parental and provider support and guidance. **B**
- Authoritative, responsive, respectful, and autonomy supportive communication should be encouraged. **B**
- Communication about the demands, expectations ("who does what") and burden of diabetes management should be continuous. **B**

2.5 | Diabetes technology

- Technological advances in insulin delivery and glucose monitoring should be available for all youth with T1D and tailored to individual wishes and needs. **B**

2.6 | Psychosocial interventions

- The interdisciplinary team should aim to provide preventive interventions for youth with diabetes and families at key developmental times, particularly after diagnosis and prior to adolescence. **A**
- These interventions should emphasize appropriate family involvement and support in diabetes management, effective problem-solving, coping, and self-management skills, and realistic glycemic expectations. **A**
- Evidence-based psychosocial, behavioral, or psychiatric interventions should be available for youth with diabetes or families exhibiting conflict, disordered communication, diabetes distress, behavioral, or psychiatric difficulties in conjunction with collaborative care with the diabetes treatment team. **A**
- Consider developmental needs of children and adolescents while planning interventions incorporating social, emotional, and tangible support. **E**

3 | INTRODUCTION

The biopsychosocial model proposes that understanding illness requires understanding the complex interactions between biology (e.g., genes, viruses), psychology (e.g., mood, behavior) and social factors (e.g., family, society).[1] Treatments must include attention to all of these domains. Being diagnosed with diabetes in childhood or adolescence can interfere with the normative developmental changes and interact with psychological and social factors in youth and their families. Integrated, collaborative care is therefore necessary. Although routine psychosocial screening in pediatric diabetes clinics effectively identifies youth struggling with psychosocial problems and facilitates referrals to appropriate care resources, screening and referral alone are not sufficient to ensure care is actually received.[2] Integrated care models ensure that youth with diabetes access mental health care.[3–5] When screening programs are initiated, there also must be a process for appropriate referrals to address identified concerns.

Here we review the main findings from studies on stress, resilience and coping, psychological and psychiatric problems, neurocognitive functioning, and integration of psychosocial assessments. We also discuss the importance of diabetes in context, including family dynamics, social support, and the diabetes team. Given the rapid

technological advances in diabetes management, we review the psychological advantages and challenges of technology. We conclude this chapter with a review of psychological and behavioral interventions in children and adolescents with diabetes. Based on these research findings, recommendations for optimal psychological care are offered and detailed in the Executive Summary (Section 2).

4 | STRESS, RESILIENCE, AND COPING

Childhood and adolescence are challenging developmental stages. Young children can get stressed navigating their social worlds, particularly family, school, and friendships.[6] Adolescence is characterized by major physical, hormonal, and psychological changes; hence it has been described as a period of stress and storm. Chronic illnesses such as diabetes exacerbate stress in children and adolescents,[7,8] and it is uncommon for children and adolescents with diabetes not to report stress.[7,9] The relationship between stress and diabetes is suggested to be bidirectional; stress can increase the risk of T2D, and living with diabetes can also cause stress.[10–13] Managing diabetes, family conflicts around diabetes management, and dealing with diabetes emotions are often a major source of stress.[8] Adversities and pandemics such as COVID-19 also accentuate stress levels in persons already affected by diabetes-specific stress. For example, the perceived increased risk of death due to COVID-19 and breakdowns in the supply chain affecting access to insulin and other supplies has contributed to anxiety and stress in the family related to diabetes care and management.[14] Stressors can be subjective and the interpretation and perception of stressors or the actual exposure to stress events vary depending on age, geography, and socioeconomic factors. In developing as well as in high-income countries, low income is a major stressor.[15,16] Race, ethnicity, and other sociodemographic factors are also associated with stress[17,18] and coping strategies.[19] Assessment of stressors should therefore be part of person-centered care.

4.1 | Diabetes distress

Diabetes distress (also referred to diabetes-related or diabetes-specific distress) is an emotional response to living with and managing diabetes. One in three adolescents with T1D,[9] one in three adolescents and young adults with T2D[20] and up to 60% of emerging adults[21] report elevated diabetes distress. Although longitudinal studies are scarce, diabetes distress also seems to persist over time.[22] Diabetes distress is best viewed as an expected emotional response to diabetes and not as a co-morbid disorder. The constant demands of diabetes management, including the relentless treatment tasks and decision-making, are key contributors to diabetes distress, particularly as these constant efforts do not always lead to the expected outcomes. Diabetes distress may negatively impact engagement with treatment, and subsequent glucose outcomes.[22] Although they can co-exist, diabetes distress differs conceptually from depression and requires a different care pathway.[23]

4.2 | Diabetes burnout

Diabetes burnout is a relatively new and not yet well-researched concept without a widely used psychometric scale. The term diabetes burnout relates to high levels of diabetes distress and/or depression that produce significant barriers to diabetes management and glycemic management.[24] It is characterized by feelings of mental, emotional and physical exhaustion of living with diabetes, leading to a detachment from diabetes and ignoring self-management responsibilities.[25] As a consequence, burnout may lead to an experience of detachment from self, support systems (e.g., years of not attending diabetes appointments) and is associated with lack of acceptance of the condition.[24] The concept is mainly described in adults with diabetes (T1D and T2D), not in children, adolescents or parents/carers. The Diabetes Burnout Scale (DBS) measures diabetes burnout specifically and was recently validated in adults.[26] Further investigation of this concept in youth with diabetes, particularly young adults and parents, is warranted.

4.3 | Resilience and coping

Diabetes Resilience is achievement of optimal diabetes outcomes (i.e., high engagement in self-management behaviors, and close to target glycemic outcomes) despite the numerous challenges inherent in having diabetes.[27] Attention to protective skills and behaviors (i.e., strengths) that promote resilient outcomes can enhance understanding of adjustment to diabetes and have implications for clinical care. These strengths include confidence or self-efficacy to manage the demands of diabetes, seeking and receiving developmentally appropriate help and support from family and others, and adaptability to handle unpredictable diabetes-related challenges (e.g., effective problem-solving and coping).[27–31] Children and families who use adaptive coping strategies such as problem-solving have a better QoL and family functioning, and report fewer depressive and anxiety symptoms.[32–36] Maladaptive coping strategies such as avoidance are associated with more significant diabetes-specific distress and suboptimal diabetes management, including fewer glucose checks and less frequent self-care behaviors.[15,34]

Evidence-based interventions for children with diabetes such as cognitive behavioral therapy and interventions that promote parental involvement, goal setting, and problem-solving[9] and reduce family conflict[37] may be helpful in promoting resilience and addressing stress. Interventions to relieve stress and enhance social support for parents/caregivers are also needed in clinical care.[37,38]

5 | PSYCHOLOGICAL AND PSYCHIATRIC PROBLEMS

Based on evidence from large, population-based cohort studies youth and young adults with T1D are about twice as likely to be diagnosed with a psychiatric disorder, especially eating, mood, anxiety and

behavior disorders, as peers without diabetes.[39–41] ADHD, personality disorders and substance use disorders (especially in males) are also more common.[39] Multi-morbidities are common: 1 in 5 youth has two or more psychiatric diagnoses.[39] Overall, psychiatric disorders are associated with abnormal self-management (e.g., insulin-manipulation) and lower QoL.[42,43]

5.1 | Disordered eating and eating disorders

Children and adolescents with diabetes have increased rates of eating disorders (ED) and disordered eating behaviors (DEB) rates compared to peers without diabetes.[44–47] These issues are especially magnified in older adolescents and young adults. Consequences of eating disorders and disordered eating include increased risk and frequency of DKA, accelerated development of vascular complications and mortality.[48,49] Even mild symptoms are relevant, as they impact self-management.[50] Population cohort studies show 1%–10% of adolescents and young adults with T1D have an ED.[39–41] Bulimia and "other specified feeding and eating disorders" are more common, but not anorexia nervosa.[51] Longitudinal studies of youth with T1D reveal that ED behaviors and symptoms are likely to persist and become more severe in young adulthood.[50,52]

ED in youth with diabetes are often associated with comorbid psychiatric disorders and sub-optimal glycemic management. Relationships between disordered eating and depression symptoms, anxiety symptoms and lower QoL in populations with T1D and T2D[53] are bi-directional. Risk factors for eating disorders and disordered eating include female gender (related to societal pressure to be thin, pubertal changes), DKA, and hyperglycemia.[54]

DEBs such as dietary restriction and intentional insulin omission[55] are more prevalent than eating disorders. In children with T1D, DEBs affect about 30%–50% of females and 10%–20% of males.[51] In youth with T2D the prevalence of DEB has been found to be about 50%.[53] Youth with T2D and DEB had a significantly higher BMI, lower insulin sensitivity, more depressive symptoms, and poorer QoL than those without DEB, with no differences between males and females.[53] A maladaptive family environment (e.g., lack of family mealtime structure, parent–child relationship quality) together with parents' personal eating attitudes (e.g., weight/shape concerns) and habits (e.g., attempts at weight loss) and negative comments about their child's weight are important when it comes to DEB in their children.[56]

DEBs often go unnoticed as adolescents and young adults refrain from being open and providers do not always feel equipped to identify and talk about them.[57,58] What usually is symptomatic and raises the attention of HCPs is frequent hospital admissions associated with DKA. Given the high prevalence and serious consequences, this calls for routine monitoring and screening of eating behaviors. A stepped approach, starting with screening with more detailed assessment following positive screens could be considered to facilitate discussion in clinical practice.[57]

5.2 | Depressive and anxiety symptoms and disorders

Initial elevation of depressive symptoms and anxiety at diagnosis is often a transitional normal adaptive response.[59] Thereafter, symptoms of depression and anxiety increase once again with longer disease duration, corresponding with the children's experience of diabetes management and implications as being more difficult and upsetting. For a smaller group of children, psychological problems persist.[59]

5.2.1 | Depressive symptoms and disorders

Youth with T1D are at an increased risk of elevated self-reported depressive symptoms compared to peers with prevalence rates ranging from 17% to 63%, depending on population, study design and diagnostic tool.[60–62] Core symptoms include low mood, no enjoyment and negative cognitions, although coexistent irritability or oppositional behavior may lead to missed diagnosis. Somatic symptoms such as fatigue and brain fog may overlap with T1D symptoms from hypo- or hyperglycemia. European population-based studies also show an increased risk of diagnosed mood disorders in youth with T1D, both in boys and girls.[39–41] Females and youth with a history of depressive episodes are especially at an increased risk. Despite the increased risk of depression, population-based studies do not find an increased risk of suicide attempts in youth with T1D compared to peers.[39,40]

Fewer studies have been conducted in youth with T2D. In the TODAY study the prevalence of elevated depressive symptoms in youth with T2D was 15%, comparable to the US population without diabetes.[63] The SEARCH study did not report prevalence rates for T2D specifically, however males with T2D were reported to have an increased risk of elevated depressive symptoms compared to males with T1D.[64] Recent studies in Canada and the US showed an increased risk of depressive disorders as well as attempted and completed suicides in youth with T2D compared to peers without diabetes.[20,65] Longitudinal studies show mixed results regarding fluctuations in depressive symptoms and glycemic changes. Within-person increases in depressive symptoms over 6 months were associated with concurrent declines in glycemic management.[66] However, 3- to 5-year longitudinal studies in adolescents and young adults with T1D did not show significant within-person associations between fluctuations in depressive symptoms and glycemic management changes.[67–69]

5.2.2 | Anxiety symptoms and disorders

Anxiety is characterized by a predominance of exaggerated fear or worry, dysfunctional coping behaviors (e.g., preoccupation or avoidance of feared situations or experiences, the use of safety behaviors to mitigate perceived threats) and adrenergic symptoms. Generalized anxiety is described as "free floating" with continual symptoms and no specific focus. There is substantial comorbidity between anxiety

and depression. As a counter to chronic uncomfortable feelings of anxiety, a person will compensate by avoiding as many stressful experiences as possible. In the context of diabetes, behaviors could include not attending appointments, checking blood glucose levels or taking insulin. Studies of anxiety symptoms in children and adolescents with T1D are mixed. Although up to 32% may have elevated anxiety symptoms, this may not be higher compared to peers without diabetes.[62,70] However, children and young adults with T1D and youth with T2D are at an increased risk for diagnosed anxiety disorders compared to controls varying from 11% to 32%.[40–43,65,71–73] The highest risk is for those with onset of diabetes between age 10 and 14 years and increasing risk with diabetes duration.[39] Children with diabetes and anxiety disorders are at risk for suboptimal glycemic outcomes, more hospitalizations, suboptimal self-management, lower QoL, more depressive symptoms and higher family conflict than peers with diabetes without anxiety disorders.[74,75]

More recent studies seem to show similar prevalence rates of depressive and anxiety symptoms and disorders as the general pediatric population, possibly reflecting the advances in diabetes treatment and awareness of mental health problems.[73,76] Nevertheless, about 1 in 7 young people with diabetes experience psychological problems, which tend to increase with diabetes duration and remain elevated in young adults with type 1 and T2D.[68,76,77] The high prevalence and the possible detrimental impact of these psychological symptoms and disorders on diabetes self-management and QoL[4,66] indicates that ongoing monitoring and screening and integration of psychological support in the care for youth with diabetes is warranted. An approach is outlined below. There should also be easy access to consulting psychiatrists for cases involving severe psychopathology and the potential need for psychotropic medications.

6 | NEUROCOGNITIVE FUNCTIONING

Growing evidence documents that children and adolescents with T1D are more at risk for pathophysiological brain changes[78–84] and neurocognitive deficits (e.g., memory, learning, and executive functioning)[82,83,85–90] than healthy peers. Although limited, research in youth T2D also shows deficits in memory and processing speed compared with youth without diabetes matched by obesity status.[91–93] Intelligence quotient (IQ) scores of youth with diabetes are statistically significantly lower than those of their peers without T1D.[82] However, IQ scores in youth with diabetes are typically well within the average range and the clinical impact might be minimal. In addition to lower IQ, youth with diabetes are at risk for specific neurocognitive deficits such as information processing difficulties (attention, memory, processing speed), learning disabilities and problems with executive functions.[82,90–93] Executive functions involve goal-oriented behavior and other key skills for self-management such as planning, problem-solving and organization. While executive function deficits can make diabetes self-management more difficult, in turn, these difficulties in self-management could lead to worsening glycemic outcomes,[94–97] which may lead to a dysfunctional cycle of further brain injury and even greater neurocognitive function deficits.[83] Additionally, worse executive functions are linked to lower QoL and mental health problems.[98–100]

Hypoglycemia, hyperglycemia and DKA, especially if recurrent, can impact school functioning and educational attainment via a combination of mechanisms including altered cognitive function and non-attendance for acute treatment.[101] However, findings regarding the impact of T1D on academic performance in young people are mixed. Older studies reported young people with T1D have lower academic performance compared to their peers or siblings without T1D[102,103] while more recent studies have not found differences in academic performance compared to peers.[104–107] There is some evidence that young people with optimal glycemic management perform better academically.[104,105,107]

Several illness-related risk factors contribute to the greater risk for these brain changes and neurocognitive deficits in youth with T1D. Early age of diabetes onset is a specific risk factor for decline in IQ over time and neurocognitive deficits.[88,108] Recent research suggests that high-time outside range (TIR), the percentage of time blood glucose levels are in the target range of 3.9–10 mmol/L (70–180 mg/dl), negatively impacts brain development in youth with T1D,[84] as does DKA, particularly at the time of diagnosis, with a decline in IQ over time and/or neurocognitive deficits.[109–111] Protective strategies have also been identified, such as improving child sleep, continued family support, reducing caregiver distress and use of diabetes technology.[82,95] Collectively, studies identified early disease onset, and factors experienced around onset (higher HbA1c, severe hypoglycemic events and DKA) as major contributors to initial cognitive decrements, and with no or limited decline in cognitive abilities if these are experienced later after diagnosis. It is hypothesized that these early disease factors provide an 'initial strike', after which the brain adapts to the new situation of fluctuating glucose levels.[112]

The SEARCH for Diabetes in Youth study found that acquired knowledge, obesity, and depression contribute to executive functioning in youth with T1D and T2D and that differences in executive functioning observed in youth with T2D compared with those with T1D are in part attributable to differences in these factors.[93] Interdisciplinary diabetes teams should be aware of risk and protective factors for neurocognitive deficits in youth with all types of diabetes. Ideally, questionnaire- or performance-based measures of neurocognitive function should be available for assessment by a mental health specialist when youth with diabetes are at risk and when they show signs of neurocognitive deficits in dealing with their diabetes self-management tasks (e.g., planning, prioritizing).

7 | PSYCHOLOGICAL ASSESSMENT: ROUTINE MONITORING AND SCREENING

Given the critical role of self-management and psychosocial factors impacting diabetes outcomes and QoL, it is imperative that psychological assessment be integrated routinely into clinical diabetes care. Validated psychological questionnaires are instrumental for screening and

assessment. Such measures can facilitate addressing relevant psychosocial needs in a dialog with the person with diabetes and their family as part of routine diabetes team consultations.[113,114] The use of these assessments is feasible and accepted by children and youth with diabetes, families and HCPs and helps focus the clinical encounter more on psychosocial factors, facilitate shared-decision making and drive care decisions instead of mainly focusing on outcomes such as HbA1c and TIR.[4,114,115] Routine assessments have been shown to positively impact well-being and satisfaction with care in young people with diabetes,[114,116,117] without direct impact on self-management and glycemic outcomes.[113,115]

Choice of assessment tool depends on the purpose, age and literacy of the person with diabetes. Children from the age of 8 years onwards are generally able to complete self-report questionnaires. In younger children, often parent-proxy measures are used, although instruments enabling the assessment of how the child is doing are available.[118–120] Generic questionnaires can be used across different populations and capture more common aspects of the person's life, allowing for comparison to normative populations. Diabetes-specific questionnaires tap into and are more sensitive to symptoms and problem areas experienced by young people with diabetes. Diabetes-specific measures should be considered for DEB assessment because generic measures might capture behaviors that are part of treatment (e.g., carbohydrate counting and calorie restriction), and adverse effects of treatment such as excessive hunger secondary to hypoglycemia. In addition, generic measures are not able to capture insulin restriction or omission to lose weight.

Several standardized and validated measures are available for providers to monitor well-being and screen for psychological difficulties of young people with diabetes.[113,121,122] Monitoring tools can track changes over time across a broad range of domains and become part of person-centered care when feedback is provided to the person with diabetes during a clinical consultation.[123] An example is routine monitoring of HRQOL which facilitates discussion between youth with diabetes and clinicians regarding psychosocial concerns as well as the different domains of HRQOL and the impact on diabetes self-management and well-being.[113,115,117] Screening tools can help identify problems that may have gone otherwise unnoticed. Often, the score is weighted based on norm scores. An example is screening for depressive symptoms, where a cut-off is used to screen for young people at risk for clinical depression.[4,124] Screening is especially of importance in adolescence and young adulthood as this is are critical developmental periods where most psychological problems first arise.[125] Routine screening for psychological difficulties from 12 years onwards, at least once a year, is recommended. Comprehensive psychosocial screening is feasible and can efficiently detect potential mental health problems and other issues impacting diabetes management.[4] Many instruments have been developed to monitor QoL and screen for psychological problems in adolescents.[113,121,126,127] Only a few instruments capture the specific developmental domains of young adults.[128]

Standardized and validated questionnaires for psychosocial monitoring, screening, and diagnosis can be used in a stepped approach with positive findings leading to further evaluation.[4,5] Starting with informal verbal inquiries for monitoring well-being and/or QoL, including mood and distress where positive responses can be probed with additional questions and/or use of standardized measures and finally by structured interviews for diagnosis. These formal diagnostic assessments and interviews should be conducted by a qualified mental health professional, familiar with the care of young people with diabetes and help guide the selection of most appropriate intervention.

Mental health specialists should train members of the health care team in screening instrument use. Further, if formal assessments are used, there must be a process for appropriate referrals to mental health specialists to address identified concerns. Screening and referral alone are not sufficient to impact clinical and psychological outcomes, nor can they ensure referrals are done so that mental health care is actually received.[2] Integrated care models are critical.[3–5]

8 | DIABETES IN CONTEXT

Diabetes self-management is most effective in the context of collaborative interpersonal relationships.[129,130] This involves the family context, peers, and diabetes team. The Social Ecological Theory and the biopsychosocial model consider the social environment or "interpersonal context of illness" as key to understanding the development and behavior of youth with diabetes to improve their health outcomes.[131,132] The interactions between youth with diabetes and their environments are reciprocal, and an individual's characteristics interact uniquely with their environment, creating a developmental context that is specific to that individual. This view helps to explain the differing developmental trajectories and outcomes of individuals with the same diagnosis of diabetes.[131]

8.1 | Impact of parental mental health

Parental well-being affects their children's outcomes. Levels of psychological distress among parents of children with diabetes are greater than parents of children without diabetes.[133] Many parents report significant distress after their child's diabetes diagnosis and have difficulty coping with their child's diabetes management.[32] Parental depression and anxiety symptoms are common in the months following diagnosis, as are symptoms of post-traumatic stress due to the new responsibilities[134–137] with nearly one in five parents reporting distress up to 4 years after diagnosis.[138] Parents of younger children report an all-encompassing impact due to constant worry and the perceived need for vigilance.[139] Fear of hypoglycaemia in parents of younger children, and distress about caring for a child with diabetes, affect parental well-being and relationships. This could, in turn, affect parenting behavior and the child's glycemic management.[17,139–142] Greater social support is associated with less stress in parents of children with recent diagnosis of diabetes.[143] Connecting with other parents caring for a child with T1D can provide valued emotional and practical support and diabetes technology use could also lessen some

burdens.[139] Literature on the specific impact of T2D in youth on parental well-being is scarce.

Parental well-being and coping also impacts their child's physical and mental health. When parents have adjustment difficulties and are greatly stressed, studies indicate they also have less diabetes management self-efficacy and their children have more behavioral and psychological problems.[144–148] Although most studies have been conducted in mothers, it is important to consider fathers as well since paternal psychological maladjustment predicted suboptimal glycemic management in children 5 years after diagnosis.[149] Further, avoidant coping in fathers was related to increased parenting stress when they were more involved in diabetes management.[150] Providing psychological support to parents is an important clinical need and helping parents can lead to more effective management of diabetes.[151,152] Parenting and family interventions can be instrumental here and will be discussed below in Section 10.

8.2 | Familial and social support

Parent support, levels of parent involvement, family conflict, parenting style, and family/parent–child relationship quality are all associated with psychological health outcomes in youth with diabetes, with some associations varying by parent gender, child age and demographic factors.[153] Continued parental involvement in diabetes care throughout adolescence and into young adulthood is beneficial[154,155] as premature transition of responsibility may be detrimental.[156] This involves parental monitoring of child behavior, which has favorable effects on youth internalizing and externalizing symptoms.[153] Especially close parental monitoring of self-management tasks requiring executive functioning skills like problem-solving and impulse control is warranted to prevent glycemic outcome declines.[95] The way parents are involved in their child's management matters. Diabetes-specific family conflict negatively affects treatment plan, glycemic management as well as QoL and depressive and/or anxiety symptoms in young people.[157] Over-involvement, or unsupportive behaviors (such as nagging), could have adverse effects.[140,158] Parenting styles are important in these family interactions. An authoritative and responsive style (i.e., clear levels of expectations for self-management and warmth and sensitivity) is associated with better self-management (e.g., checking blood glucose levels more frequently, making healthy food choices) and glycemic management, and less overweight (therefore perhaps preventive for T2D); conversely, more psychological control is associated with suboptimal outcomes.[155,159] The benefits of an authoritative parenting style transcend ethnicity, socioeconomic status, and household composition.[159] Studies that explored relationship quality and child psychological health generally found that more cohesive family relationships were associated with lower youth externalizing symptoms. There may be a relationship between higher quality family relationships and lower internalizing in youth with T1D, especially for youth of color.[153] In addition, a warm and accepting environment is associated with better physiologic and psychosocial outcomes.[154,158]

Although most research on the social context of youth with diabetes has focused on the family environment, as children get older (particularly during adolescence) peer relationships become more important. Supportive friends can complement parents' involvement in psychological outcomes[160,161] with youth receiving instrumental support from their families and also considerable emotional support from their friends. On the other hand, social conflict and greater orientation toward peers negatively affects diabetes outcomes.[161,162] When youth attribute negative peer reactions to their self-management (e.g., joking about being a "junkie" when administering insulin), they are more likely to have difficulties being consistent with their treatment plan and have increased diabetes stress, which in turn worsens glycemic management. Overall, the research linking peer relations to diabetes outcomes is mixed. Although qualitative studies reveal that adolescents believe peers have an impact on their diabetes, the quantitative findings are inconclusive.[162]

8.3 | Communication

Pediatric diabetes care is characterized by a triadic relationship.[163] Youth, parents and pediatric care providers must sustain effective communication about the demands, expectations ("who does what") and burden of diabetes management[164] as youth face many physical and psychosocial developmental changes from childhood to adolescence, as responsibility for diabetes management gradually shifts from parents to youth. Providers need to navigate this shift by being attuned to youth's evolving competencies and readiness for independent self-care,[165,166] while also considering the need for parental and provider support and guidance. Research has shown that responsive and supportive communication between youth with diabetes and their family, caregivers and the broader social environment (e.g., peers, school system, other relatives, sport coaches) is essential for youth well-being, including better glycemic outcomes, self-management, QoL, and satisfaction with care.[117,129,130,167] Person-centered communication by providers, which is closely linked to autonomy-supportive communication (i.e., explaining the personal relevance of treatment guidelines and offering choices),[130,163,168] puts the young person with diabetes and their family at the forefront by eliciting their perspectives on the proposed treatment recommendations, and by engaging in a shared-decision making process. This communication style promotes openness and trust, and fosters dialog about the best way to optimize diabetes management and outcomes for each young person with diabetes and their family.[168] Clinically, person-centered communication includes elements of motivational interviewing. At the core of motivational interviewing are reflective listening, being empathic, not engaging in arguments or persuasion and focusing on changing behavior and enhancing self-efficacy.[168,169] In clinical practice, communication is an effective, modifiable tool to enhance diabetes self-management and to establish a constructive relationship between providers, youth with diabetes, and their families.

8.4 | Diabetes team

Given the burden of living with a chronic illness and the greater incidence of mental health problems in youth with diabetes compared to their peers, psychosocial care should be an integral part of the collaborative, person-centered medical care for youth with diabetes. The Collaborative Care Model (CCM) has emerged as a promising clinical model to facilitate the integration of mental health care with physical health care to simultaneously address co-occurring physical and mental health problems.[5,170] The shared goal of care should be to optimize health outcomes and QOL. Easy access to mental health professionals such as psychologists, social workers and psychiatrists must be available.[121] These mental health professionals should have training in diabetes and its management, have expertise in the mental and behavioral health of youth, and be available to interact with youth with diabetes and families at clinic visits to conduct screening and more complete assessments of psychosocial functioning on a regular basis. In addition, the mental health professionals should support the diabetes team in the recognition and management of mental health and behavior problems. In case of severe psychopathology and the potential need for psychotropic medications, referral to a psychiatrist is indicated.[171]

9 | DIABETES TECHNOLOGY

Technological advances in diabetes care have changed the way many persons manage diabetes in the last two decades, and in some countries more than half of children and adolescents use insulin pumps and continuous glucose monitoring (CGM).[172,173] Developments such as insulin pumps, real time and intermittent scanned CGM and automated insulin delivery systems improve diabetes management, health outcomes and reduce frequency of hypoglycaemia in the majority of those using them.[174] Technology uptake is increasing most especially in the pediatric population.[172,173] CGM use is also now considered to be "standard of care" for people with T1D and is recommended by the EASD/ADA Clinical Consensus Report 2021 to manage T1D.[175]

Psychological benefits associated with use of diabetes technology, especially CGM use, usually include improved QOL, reduced diabetes distress, reduced fear of hypoglycaemia, as well as "better sleep, safety and flexibility," QOL, family functioning and stress in both youth and their caregivers.[176–178] The widespread migration from self-monitoring of blood glucose (SMBG) to CGM has greatly increased the amount of real time blood glucose information available to parents and youth. For insulin pump therapy, the evidence regarding QOL benefits are not that clear.[179,180] These studies are, however, limited by small sample sizes as outlined in systematic reviews. The consensus statement on insulin pump use in children and adolescents states that QOL with insulin pump therapy is similar to, or higher than of children and adolescents using MDI.[179,181] The benefits are more obvious from the emerging evidence on automated insulin delivery systems: these improve clinical outcomes (TIR, HbA1c, reduction in the number of hypoglycemic events),[182,183] and also enhance QOL, reduce diabetes distress, and improve sleep quality in children and caregivers.[184,185]

Some psychological disadvantages of diabetes technology adoption have been reported, including issues with body image,[186] disruptive alarms and painful insertions.[176] The large amount of data and real-time remote glucose monitoring can be a source of conflict between children with T1D and their parents, as deviations from recommended diabetes management are more readily and immediately noticeable to caregivers. The research literature, however, does not demonstrate any evidence of increased family conflict following CGM introduction.[187–189] There even might be a reduction in family conflict after the commencement of CGM.[178,190] Anecdotal evidence from diabetes clinics often lists "body image" as an obstacle to technology adoption, as some people with diabetes (adolescents, young adults), "do not want to have anything attached to their bodies."[191] However, according to a systematic review on this topic, there were no differences in body image between those with T1D using and not using technology (insulin pumps, CGM).[192] Frequent exposure to device alarms (in particular false or unnecessary ones) for a device user or a caregiver can result in poor or interrupted sleep and/or unwelcome distractions, as well as "alarm fatigue," when, over time, the user becomes less likely to respond to true alarms.[192–194] These disadvantages of technology used in diabetes management are usually listed as barriers to its adoption, and rarely, these might be the reasons to discontinue pump or CGM. Evidence from the T1D Exchange, US-based diabetes registry, highlights that the overall insulin pump discontinuation was 3%. Those who discontinued insulin pump therapy were more likely to have higher HbA1c levels at baseline, and the most frequently listed reasons for discontinuation were problems with wearability (57%), disliking the pump or feeling anxious (44%).[195] Therefore, the fears and obstacles should be acknowledged and discussed with adolescents with T1D and their parents/carers, and advantages should be carefully explained, so the family can make an informed decision about whether to use a device.

Little information is available regarding the use of diabetes technology in youth with underlying mental health issues. Registry-based data from the German and Austrian DPV diabetes registry showed that the use of CSII was more common in youth with depression, anxiety disorders, or needle phobia compared with people without any mental health issues. On the other hand, those with psychotic disorders least frequently used insulin pumps, and those with eating disorders and ADHD had similar levels of uptake.[196] There is some indication that the use of pumps is associated with fewer disordered eating behaviors because of the flexibility a pump provides[197]; however youth with ED or depression are more likely to discontinue pump use than children without co-morbid mental health conditions.[196]

10 | PSYCHOSOCIAL AND BEHAVIORAL INTERVENTIONS

There is a substantial literature addressing psychosocial and behavioral interventions for the treatment of children and adolescents with

T1D. Systematic reviews including meta-analyses have shown the efficacy of various approaches[198–200] including family based interventions.[38,201] While methodological limitations have been noted,[198,202–205] it can generally be concluded that there is a solid evidence base for psychosocial and behavioral interventions[206] although the effects on glycemic outcomes are inconsistent.[202] Many children and adolescents receive psychosocial interventions, as demonstrated by a nationwide study in Germany that revealed approximately 30% receive psychosocial support. These youth had suboptimal glycemic management but with continued psychosocial support, this remained stable over time.[207] A recent study documented that having pediatric psychologists integrated with the interdisciplinary health care team has benefits for youth as well as insurers: youth who met with psychologists during their clinic visit had better subsequent glycemic management and reduced health care costs.[208] It should be noted that almost all research has been conducted in children and adolescents with T1D and the evidence-base in young adults and youth with T2D is scarce.[209,210]

10.1 | Family based interventions

Family based interventions show improved psychosocial outcomes for youth and families such as reducing family conflict and improved parent–child relationships, but mixed results for glycemic outcomes.[211,212] Family based, behavioral interventions include goal-setting, problem-solving, self-monitoring, parental praise for regimen-related behaviors, use of behavioral contracts, clear and consistent parental communications, and appropriately shared responsibility for diabetes management tasks. Behavioral family systems therapy with diabetes-specific tailoring reduced family conflict and improved ability to be consistent with treatment plans, with improved glycemic management over 18 months, by means of improved parent-adolescent communication and problem-solving.[213] It is important to provide psychosocial interventions during the period after diagnosis as this is a stressful time for the child and the family. Several interdisciplinary programs for newly diagnosed children have been reported to improve child and parental outcomes.[214–218]

10.2 | Psychosocial interventions during clinic visits

One approach is to deliver brief psychosocial interventions during routine clinic visits. Family teamwork could help to increase positive parental involvement, reduce family conflict and help prevent worsening of glycemic management in younger youth.[219–222] Improving problem-solving and communication skills, and appropriate sharing of responsibility for diabetes management showed improvements in glycemic management and parental involvement. Similarly, a psycho-educational intervention addressing various diabetes management issues delivered by a "care ambassador" at regular outpatient clinic visits, resulted in reduced hypoglycemia and emergency department visits.[223]

10.3 | High-risk individuals

Other studies have targeted psychological interventions to youth at high risk for worse health outcomes, such as low income, ethnic and/or racial minority adolescents with chronically sub-optimal glycemic management. Intensive home-based multi-systemic therapy that addressed the individual adolescent, the family system, and the broader community systems (i.e., school and health care system) seem most successful here in improving blood glucose monitoring and glycemic management, and reducing health care utilization and medical costs.[224,225] The subgroup of youth with chronically suboptimal glycemic management is a high-risk population that requires novel approaches to intervention.[226] High-intensity frequent contact with these youth through various means of communication may be necessary to improve diabetes management outcomes.[227,228]

10.4 | Peer group interventions

Another approach to psychosocial intervention involves peer groups.[229,230] In adolescents as well in younger, school-age children, coping skills training have a positive effect on glycemic management and QOL,[231–234] reduced diabetes-related stress,[235,236] improved social relationships.[237] A recent Chinese study showed that coping skills training was more effective for younger than older youth.[238]

10.5 | Interventions with individual participants

Other psychosocial interventions have addressed individual youths. Cognitive behavior therapy for youth with diabetes is one of the most well researched therapies, and feasible and acceptable, with improvements noted in psychosocial functioning.[202,239] As research has shown that higher levels of intrinsic motivation for management tasks improves diabetes management, glycemic management, and psychosocial functioning,[240] motivational interviewing is designed to increase this intrinsic motivation. Indeed, motivational interviewing delivered by a psychologist is shown to improve long-term glycemic management and QoL,[241] especially in older adolescents.[242] It should be noted that these types of interventions are generally delivered by a mental or behavioral health professional trained in this approach. Motivational interviewing delivered by trained non-psychologist HCPs who did not show improved glycemic management,[243] likely due to inadequate training and counseling skills.[244] Motivational intervention combined with problem-solving training resulted in significant improvements in motivation, problem-solving, diabetes management, QOL, and reduced family conflict, but not glycemic outcomes.[245] A motivational intervention delivered by a nurse during home visits for adolescents with suboptimal glycemic management showed a positive effect on glycemic management over 6 months.[246] Another approach, to increase external motivation for diabetes management, is to use monetary reinforcement to improve youth performance using a hybrid closed loop system,[247] suggesting behavioral economics may be a

feasible way to improve self-management behavior. Another approach to psychosocial interventions with individual youth targets distress and depression prevention by promoting resilience. A large RCT examined the impact of an eight-session diabetes distress and depression prevention program for adolescents (STePS). Adolescents reported significant reductions in diabetes distress and depressive symptoms after 1 and 3 years.[248] Recent intervention research has employed several innovative approaches, such as mindfulness-based stress reduction or gratitude.[249,250]

10.6 | Internet-based and digital interventions

Problem-solving skills training and coping skills training can both successfully be delivered via the Internet, showing positive outcomes.[251,252] Further, adolescents respond well to behavioral intervention using Skype,[228] tele-health,[253] text messaging,[227,254] and can receive social support via chat rooms.[255] Also more complex interventions, such as an multicomponent motivational and cognitive intervention targeting youth with suboptimal glycemic management and emotional regulation difficulties, can be delivered via the Internet as it resulted in increased frequency of blood glucose monitoring, improved working memory, and improved glycemic management[256]; youth with more emotional control problems benefited the most from this approach.[257]

Digital health interventions (i.e., programs or tools which use digital technology to encourage or foster behavior change, such as websites, mobile applications [apps], text messaging, or online games) for youth with diabetes have some impact on their mental health such as self-efficacy, but few consistent effects for other psychological, behavioral, or health outcomes; results also indicated studies showed high risk of bias and more research was needed using theory-based approaches with stronger methodologies.[258]

10.7 | Interventions for parents

Parents often need additional coping supports. Parenting interventions in parents of children and adolescents with T1D could significantly reduce parents' depression and distress, and help them ask for positive social support.[38] Coping skills training for parents of young children may be helpful.[259] Interventions to reduce distress and fear of hypoglycemia in parents are under development.[260–262]

In summary, the results of controlled intervention research for individual and family based interventions show promising effects with respect to psychosocial outcomes and inconsistent results for glycemic outcomes. Future work should investigate which key intervention components may be attributed to positive diabetes outcomes. It should consider the competency of the interventionists delivering the therapy and match psychological approaches to a person and their life course. There is growing evidence supporting the use of the Internet and other digital approaches to deliver behavioral interventions, and a need for higher quality studies. In general, psychosocial and behavioral intervention research is limited by not including enough high-risk youth (i.e., low income, ethnic minority, single parent youth) in their study samples.[263,264] In addition, there is a need for more studies specifically targeting youth with T2D and young adults. There are also opportunities for more research using clinic-based brief interventions during routine care that focus on improved self-management and reduction of diabetes distress, which could have the potential to maximize reach and impact through scalability.[265]

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13428.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: de Wit M, Gajewska KA, Goethals ER, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Psychological care of children, adolescents and young adults with diabetes. *Pediatr Diabetes*. 2022;23(8):1373-1389. doi:10.1111/pedi.13428

Accepted: 5 November 2022
DOI: 10.1111/pedi.13451

ISPAD GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Glucose monitoring

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KEYWORDS: adolescents, CGM, children, continuous glucose monitor, diabetes technology, T1D, type 1 diabetes

SUMMARY OF WHAT IS NEW OR DIFFERENT

Since publication of the 2018 guidelines, the area of glucose monitoring has evolved, especially as regards continuous glucose monitoring (CGM) systems. CGM is more widely available in many parts of the world; latest generation devices are factory-calibrated, more accurate, and do not need a confirmatory fingerstick blood glucose measurement. More studies regarding the efficacy of CGM systems, irrespective of the type of insulin delivery, are available including long-term observational studies. With increased availability and wider use, practical considerations related to daily CGM use (e.g., skin issues, physical activity) as well as educational and psychosocial aspects have come to the fore, which are also addressed in this chapter.

EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Regular self-monitoring of glucose (using accurate fingerstick blood glucose [BG] measurements, real-time continuous glucose monitoring [rtCGM] or intermittently scanned CGM [isCGM]), is essential for diabetes management for all children and adolescents with diabetes. **A**
  - Each child should have access to technology and materials for self-monitoring of glucose levels and sufficient supplies to optimize diabetes care. **B**
  - When fingerstick BGs are used, testing may need to be performed 6 to 10 times per day to optimize glycemia. **B**
  - Frequency of BG testing correlates with improved HbA1c levels and reduced acute complications. **B**
  - Regular review of glucose values should be performed to inform adjustments to medication/nutritional therapies to optimize glycemia. **B**
  - Diabetes center personnel should advocate to nations, states, and health care funders to ensure that children and adolescents with diabetes have adequate glucose monitoring supplies. **E**
- Providers should be aware of the differences in accuracy among BG meters—only meters that achieve international accuracy standards (ISO 15197:2013 or are FDA-approved) should be used. **E**
- Use of CGM is strongly recommended in all children, adolescents, and young adults with type 1 diabetes (T1D). **A**
- Where available, CGM should be initiated in all children, adolescents, and young adults with T1D as soon as possible after diagnosis to improve glycemic outcomes. **B**
- isCGM, also known as flash glucose monitoring, in the pediatric population is safe, may improve time in range (TIR) and HbA1c levels, decreases time in hypoglycemia, and lowers glycemic variability. **B**
- For isCGM, higher scanning frequency (11–13 scans/per day) is associated with more favorable glycemic markers (HbA1c and TIR). **B**
- rtCGM can be effectively used to lower HbA1c levels, reach target HbA1c level, reduce glucose variability (for insulin pumps, closed-loop systems, and multiple daily injections [MDI]), increase TIR, reduce mild to moderate hypoglycemia and shorten time spent in hypoglycemia in the pediatric population with T1D. **A**
- rtCGM data can particularly benefit children who cannot articulate symptoms of hypoglycemia or hyperglycemia and those with hypoglycemic unawareness. **A**
- The effectiveness of rtCGM in children and adolescents with T1D is related to the amount of time the sensor is used. **A**
- Prior to CGM start, portray the use of diabetes devices and technologies as an option that can be a good fit for many youth and families; provide education and encourage youth and families to review vetted websites and device informational materials. **E**
- Structured initial and ongoing education and training in CGM use (including data review) is paramount to successful adoption and continued use of this technology. **E**

TABLE 1 Comparison of ISO 15197:2013 and FDA BG meter accuracy standards

Setting	ISO 15197:2013[5]	FDA[6,7]
Home use	95% within 15% for BG ≥100 mg/dl 95% within 15 mg/dl for BG <100 mg/dl	95% within 15% for all BG in the usable BG range[b] 99% within 20% for all BG in the usable BG range[b]
Hospital use	99% in A or B region of consensus error grid[a]	95% within 12% for BG ≥75 mg/dl 95% within 12 mg/dl for BG <75 mg/dl 98% within 15% for BG ≥75 mg/dl 98% within 15 mg/dl for BG <75 mg/dl

Abbreviations: BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization.
[a]The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error).
[b]Values outside of the "clinically acceptable" A and B regions are considered "outlier" readings and may be dangerous to use for therapeutic decisions.[8]

- Setting realistic expectations for the integration of diabetes technologies is paramount to ensure the success of persons and caregivers adopting new technologies. **B**
- It is critical to counsel youth/families and identify potential barriers to adoption of new technologies or continued use of devices. Validated person-reported outcome measures can help to identify barriers. **B**

1 | INTRODUCTION

Self-monitoring of glucose has a pivotal role in the management of insulin-treated children and adolescents with diabetes. It tracks immediate and daily glucose levels including periods of hypo- and hyperglycemia, helps guide insulin dose adjustments, facilitates evaluation of therapy responses and achievement of glycemic targets in a safe and effective manner.

Along with major clinical trials demonstrating the superiority of intensive insulin therapy in persons with T1D in the early 1990s,[1] self-monitoring of capillary blood glucose (SMBG) using hand-held portable meters in combination with glucose test strips and a lancet became the most widely used method of glucose monitoring, replacing urine glucose testing.

In recent years, systems for continuously monitoring interstitial fluid glucose concentrations, CGM, using subcutaneously placed glucose sensors have become standard of care in T1D in many countries, particularly for children, adolescents, and young adults,[2] and have been successfully employed for insulin-treated type 2 diabetes.[3]

The purpose of this chapter is to review and update the evidence on glucose monitoring devices (i.e., SMBG and CGM) in children, adolescents, and young adults and to provide practical advice and approaches to their use.

TABLE 2 Factors that alter BG measurements

Glucose oxidase monitors	
Substances that decrease readings	*High ambient oxygen*
	Uric acid
	Acetaminophen
Substances that increase readings:	*Low ambient oxygen*
Substances with variable effect:	*L-DOPA*
	Ascorbic acid
	Tolazamide
Glucose dehydrogenase monitors	
Substances that increase readings:	*Galactose*
	Xylose

Abbreviation: BG, blood glucose.

2 | SELF-MONITORING OF CAPILLARY BLOOD GLUCOSE

Early SMBG measurement methods relied upon reflectance assays coupled with oxidation of glucose allowing for a colorimetric readout. Currently available glucose meters use an electrochemical method with an enzyme electrode containing either glucose oxidase or glucose dehydrogenase.

2.1 | Meter standards and accuracy

There is considerable variation in the accuracy of widely-used BG monitors.[4] Most reliable data are provided by meters meeting current international accuracy standards. The two most used standards are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the U.S. Food and Drug Administration (FDA) (Table 1). ISPAD recommends exclusive use of glucose meters that achieve these standards. Health care professionals should choose and advise on meters that are accurate and familiar to them as well as affordable to the person with diabetes.

The specified accuracy standard achieved during controlled conditions might vary significantly from actual SMBG meter performance in real-world settings.[4] Detailed information on the actual performance of SMBG devices is provided by The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program (www.diabetestechnology.org/surveillance/).

SMBG accuracy depends on proper hand washing with complete drying[9] and requires proper blood application and use of adequately stored, unexpired test strips, which are not counterfeit nor preowned/second hand.[10] Providers and persons with diabetes/caregivers need to be aware of additional factors that can impair meter accuracy: Due to the enzymatic electrochemical reaction, monitors are sensitive to temperature and have a defined operating temperature range.[10] Typically, an error message is displayed if the temperature is out of range. Unlike glucose dehydrogenase-based meters, glucose oxidase meters are sensitive to the ambient oxygen and should only be used with capillary blood of people with normal oxygen saturation. Low oxygen tensions (i.e., high altitude, hypoxia, venous blood readings) may result in falsely high glucose readings, higher oxygen tensions (i.e., arterial blood) may lead to falsely low readings.[10] There are also several substances that may interfere with glucose readings (Table 2).[10]

2.2 | Expert meters

Expert BG meters have integrated bolus advisors to calculate insulin dosages. Randomized controlled trials (RCTs) have shown use of a bolus calculator significantly increases the number of people achieving HbA1c targets and reduces hypoglycemia.[11–13]

2.3 | Frequency and timing of SMBG testing

SMBG frequency correlates with improved HbA1c levels and reduced acute complications.[14–16] Generally, SMBG should be performed at a frequency to optimize each child's diabetes. For persons using intensive insulin regimens (multiple daily injections of insulin pump therapy), SMBG testing should be performed:

- during the day, prior to meals and snacks,
- at other times (e.g., 2–3 h after food intake) to determine appropriate meal insulin doses and show levels of BG in response to the action profiles of insulin (at anticipated peaks and troughs of insulin action)
- to confirm hypoglycemia and after treating low BG to monitor recovery
- at bedtime, as needed overnight and on awakening to detect and prevent nocturnal hypoglycemia and hyperglycemia
- prior to and while performing potentially hazardous tasks (e.g., driving)
- In association with vigorous exercise (before, during, and several hours after physical activity)
- during intercurrent illness to prevent hyperglycemic crisis.

Successful intensive insulin management requires at least 6 to 10 checks per day, appropriate response to the observed values, and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan.[15] This includes review by the person with diabetes and their caregivers/family in addition to consultation with the diabetes care team.

However, the actual number and regularity of fingerstick BG measurements should be individualized depending on:

- type of insulin regimen
- ability of the child to identify hypoglycemia
- availability and affordability of meters and test strips

In resource-limited settings, availability and affordability of glucose meters and test strips are not guaranteed. Even though many

children are on multiple daily injection regimens, only a few can afford frequent BG testing needed to optimize diabetes management. Very often testing is performed 3–4 times a day (i.e., pre-breakfast, pre-lunch, pre-dinner, and at bedtime). However, many persons with diabetes must resort to two times daily, that is, before breakfast and before dinner. If there are no BG monitoring capabilities, then urine testing is performed. For a comprehensive discussion on aspects of diabetes management in resource-limited settings, including glucose monitoring, please refer to the ISPAD 2022 Consensus guidelines Chapter 25 on 'Management of Diabetes in Children and Adolescents in Limited Resource Settings.

3 | CONTINUOUS GLUCOSE MONITORING

Rapid, capillary assessments of BG concentrations have been instrumental in permitting achievement of recommended targets over the past 30 years. However, SMBG only provides single snapshots of glucose concentrations. Consequently, episodes of hyper- and hypoglycemia, in particular nocturnal and asymptomatic episodes, as well as considerable fluctuations in BG concentrations may be missed and therefore not factored into treatment decisions.

The emergence of CGM in the late 1990s represented a significant therapeutic milestone. Instead of single-point measurements of capillary blood glucose concentrations, CGM devices measure interstitial glucose concentrations subcutaneously at 1–15 min intervals using enzyme-coated electrodes or fluorescence technology. Significant improvements in device technology over the past decade (including improved accuracy, approval for non-adjunctive use, and reduced need for calibration), availability, smaller size, remote monitoring capability, and overall personal acceptance of CGM systems have contributed to the widespread adoption of this technology in clinical practice.

3.1 | CGM use and uptake

In many countries, CGM use has now become the standard of care for people with T1D.[2] According to data from German and Austrian DPV and U.S. T1D Exchange registries, CGM use increased exponentially from 2011 to 2017 in all pediatric age-groups (DPV: 4% in 2015 to 44% in 2017; T1DX: 4% in 2013 to 14% in 2015 and to 31% in 2017), with the highest use among preschool-aged and early school-aged children.[17] From 2017 to 2020, further increase in CGM use among individuals with diabetes aged <25 years was seen in both registries each year for all age ranges (DPV: 40% in 2017 to 76% in 2020; T1DX: 25% in 2017 to 49% in 2020).[18] Recent data from the Australasian Diabetes Database Network (ADDN) registry and the Australian National Diabetes Service Scheme (NDSS) demonstrate 79% of registry participants with T1D aged <21 years are using CGM.[19]

DPV and T1D Exchange registry data indicate significant disparities in CGM use by socioeconomic status (SES). Of note, in the T1D Exchange registry, the gap of device use between highest and lowest SES quintiles (52.3% vs. 15.0%) was more pronounced than in the DPV population (57.1% vs. 48.5%).[20] Adequate clinic-specific resources and interventions to identify and overcome barriers to CGM uptake are necessary to promote CGM adoption and continued use.[21] In a multiclinic quality improvement initiative of the T1D Exchange Quality Improvement Collaborative, center-specific interventions consisting of active person support and education, training and education of the clinical team, as well as interaction with insurance companies and vendors led to increases in CGM use from 34% to 55% in adolescents and young adults over 19–22 months.[21]

3.2 | Categories of sensors

CGM systems fall into one of the following categories:

1. Blinded CGM or professional CGM;
2. Real-time CGM;
3. Intermittently scanned CGM (isCGM) or Flash CGM;

Blinded/retrospective/professional CGM

Blinded or professional CGMs were the first widely used CGM devices, for example, the MiniMed CGMS Gold system (Medtronic MiniMed, Northridge, CA) released by Medtronic in 1999. Professional CGM systems obtain short-term glucose data which are not visible to the user. They provide health care professionals with data showing glucose excursions and patterns. In addition to clinical practice, professional CGM systems are sometimes employed in research settings to obtain retrospective glucose data and to reduce potential bias (e.g., in certain settings people may deviate from their usual behavior when seeing their CGM readings in real-time).

Real-time CGM

Real-time CGM (rtCGM) systems automatically display glucose values at regular intervals and can utilize programmable alarms when sensor glucose levels reach predefined hypo- or hyperglycemia thresholds, as well as rate-of-change alarms for rapid glycemic excursions. Many commercially available rtCGM systems transmit glucose data directly to smartphones. These data can then be stored and retrieved on a web server ("cloud") and used for remote monitoring purposes by caregivers and healthcare professionals.

In addition to traditional, self-inserted transdermal sensors with a lifetime from 6 to 14 days, a long-term implantable sensor for up to 6-month use is available (Eversense, Senseonics Inc., Germantown, MD) that received regulatory approval in the European Union (Conformitè Europëenne [CE] Mark) in 2016 and subsequently in other regions. Of note, the Eversense CGM is currently approved only for use in adults over 18 years of age. Its implantation requires a minor in-clinic procedure performed by a trained physician or a nurse practitioner. Unlike traditional CGM sensors, where glucose is measured using the enzyme-based electrochemical method, the Eversense implantable sensor uses non-enzymatic optical fluorescence. The next-generation Eversense CGM has 180-day long-term wear time with daily calibration.[22]

Intermittently scanned CGM

In 2014, the FreeStyle Libre Flash Glucose Monitoring System (FSL) (Abbott Diabetes Care, Alameda, CA) was introduced representing a different CGM category: intermittently scanned CGM (isCGM). IsCGM devices do not automatically display glucose values at regular intervals, but report glucose levels only when the user scans the sensor by holding a reader, or a near field communication protocol (NFC)-enabled smartphone, close to or over the sensor. Current interstitial glucose levels and glucose trend arrows as well as a graph of current and stored glucose readings are provided on demand.[23] As with rtCGM, glucose data from isCGM can be transferred from a smartphone to a webserver for remote glucose monitoring purposes by caregivers or health care professionals. The sensor can provide glucose values up to 14 days after a 1-h sensor warm-up period.

The second generation of FreeStyle Libre (FSL2) was approved in Europe in 2018 and in the USA in 2020. FSL2 sensors have higher accuracy (mean absolute relative difference [MARD] 9.2% and 9.7% for adults and children,[24] respectively) and, in addition to the general FSL capabilities, have optional alarms to alert persons in case the glucose level is out of the target range. To see the actual level, the user must scan the sensor. The third generation, the FSL3, is actually a rtCGM providing real-time alarms and real-time readings without the need to scan. It received CE marking in 2020.

3.3 | Accuracy of CGM devices

The accuracy and precision of first generation CGM systems were notably inferior to those of capillary BG monitors. Over the past 10 years, however, there has been continued improvement in the accuracy. Discrepancies between actual BG and CGM levels, however, continue to occur in the hypoglycemic range and when glucose levels are changing rapidly. To a great extent this is due to the physiological delay of about 5–10 min between the flow of glucose from the intravascular to interstitial compartments.[25] Accuracy is also influenced by the time it takes for the sensor to react to glucose[26] and the use of digital filters for smoothening of the sensor signal during conversion of the measured sensor signal into a glucose value.[26,27] Sensor performance also may be affected by biomechanical factors such as motion and pressure (typically micro-motion and micro-pressure).[28]

Methods used to assess the accuracy of CGM systems include the mean absolute relative difference (MARD) between sensor readings and reference BG values (absolute difference divided by the reference value, expressed as percentage) and error grid analysis. MARD is currently the most common metric used to assess the performance of CGM systems. Of note, MARD has its limitations, and its use as the sole performance parameter for CGM systems must be viewed critically.[29] The lower the MARD, the closer CGM readings are to the reference glucose values. Error Grid analysis allows one to assess clinical significance of the discrepancy between the sensor and the reference glucose measurement; greater accuracy corresponds to a higher percentage of results in Zone A and B. Accuracy continues to improve with each new generation of CGM sensors and systems. For most commercially available CGM systems, the accuracy in clinical trials reached 8%–10% MARD with about 99% of glucose readings within the clinically acceptable error Zones A and B.[24,30,31] It should be noted that in the home-use setting CGM system may produce higher average MARDs than during in-clinic studies.[32]

Unlike BG meters (see Table 1), for CGM, the minimum accuracy requirements have not been determined until recently, and there are no consistent standards in the approval of CGM systems, particularly in relation to the provision of clinical data demonstrating the device's accuracy in the intended use population, as well as transparency and access to this data. Recently, the FDA has outlined a new 510 K (premarket approval) route for some CGM systems, designated as "integrated CGM" (iCGM) with additional special controls governing accuracy ability of this device to work with different types of compatible diabetes management devices, including automatic insulin dosing systems, insulin pumps, and BG meters.[33]

3.4 | Sensor interference

Certain exogenous and endogenous interstitial fluid substances, including some commonly-used medications, may interfere with CGM system accuracy. This can result in falsely high or low glucose values.

In particular, therapeutic doses of hydroxyurea can markedly elevate sensor glucose readings compared with glucose meter values[34]; likewise, acetaminophen at a dose of 1000 mg can falsely elevate sensor glucose values in certain CGM systems.[35,36] Salicylic acid at doses ≥650 mg may mildly reduce glucose readings, and ascorbic acid (vitamin C) at doses ≥500 mg may cause falsely higher readings.[37] CGM readings may also be affected by ingestion of lisinopril, albuterol, atenolol, and red wine.[38]

The effect of different substances on glucose reading depends on sensor technology. Specifically, CGM systems that use enzymatic electrochemical sensors to measure glucose concentrations seem to be more susceptible to interference than systems using abiotic (non-enzyme based), fluorescent glucose-indicating polymer to measure glucose. In particular, for the long-term implantable fluorescence-based sensor only tetracycline and mannitol produced significant sensor bias when tested in vitro within therapeutic concentration ranges.[39]

Medications such as salicylic acid, acetaminophen and vitamin C, commonly available over the counter for self-administration, and may be present in combination products or supplement formulations leading to persons with diabetes not knowing that they are taking specific substances. Sensor bias produced from various substances can be most significant for persons using CGM data without confirmatory measurements of capillary BG or for those using CGM data to inform insulin delivery in closed-loop systems. Therefore, CGM users should be aware of how certain systems may be impacted by common medications and always test with a glucose meter whenever symptoms do not match a CGM reading.

3.5 | Calibrations/factory-calibrated systems

The latest generations of rtCGM systems (i.e., Dexcom G6, Dexcom G7, Guardian 4) and all available isCGM (FSL1, FSL2) are factory-calibrated, meaning that user calibrations using fingerprick glucose measurements are generally not needed. This eliminates pain and inconvenience and takes away a significant source of error from sensor calibration. Factory calibration is performed under laboratory conditions during the sensor manufacturing process.[40] For rtCGM manual calibration is still possible, for example, if CGM readings and results from capillary BG readings do not line up well over a prolonged period of time.

For older generation CGM sensors that depend on manual calibrations (i.e., entering BG readings from a meter into the CGM system), the required calibration frequency varies by device. Typically, the first calibration is performed 1–2 h after insertion of the sensor and thereafter a minimum of one calibration is required every 12 h. For these systems, regular calibrations are essential to maintain the accuracy and optimum sensor performance. The optimum times to calibrate are when the interstitial fluid glucose concentration is in equilibrium with the capillary blood, i.e. when glucose levels are least likely to be changing rapidly: before meals, before bedtime, before insulin administration, when trend arrows on the CGM/pump screen show glucose levels are stable. User calibration can lead to wrong sensor reading if at the time of calibration the sensor signal has a temporarily falsely reduced or elevated value, for example, caused by interfering substances or site compression ("compression lows").[40]

3.6 | Non-adjuvant use

RtCGM systems were originally approved for adjunctive use, meaning the sensor glucose results needed to be verified by capillary SMBG before taking action (e.g., insulin dosing). Along with significant improvements in accuracy, more and more sensors have received approval for non-adjuvant use, that is, diabetes-related decisions and insulin dosing are made based on CGM values alone.

Studies utilizing computer modeling have shown that the threshold MARD level of ≤10% is safe for non-adjuvant use of CGM[41] and most currently-available commercial CGM systems meet this condition. Furthermore, the T1D Exchange REPLACE BG study provided evidence of the safety and effectiveness of non-adjunctive sensor use.[42]

Dexcom sensors (G5 and G6™ Mobile CGM, Dexcom, San Diego, CA) have received FDA and CE approval for non-adjunctive use in persons aged 2 years and older. The Abbot Libre Flash Glucose Monitors (Abbott Diabetes Care, Alameda, CA) have received FDA and CE approval for treatment decisions in persons aged 4 and older. The Medtronic Guardian 4 sensor is CE marked for nonadjunctive use from the age of 7 years. Fingerprick testing may still be recommended under certain circumstances: hypoglycemia, if glucose is changing rapidly, and especially if symptoms are not concordant with the system readings.

Efficacy of CGM

Real-time CGM systems

Early-generation rtCGM systems use for children with T1D was associated with only modest benefits in glycemia when compared with SMBG.[43–45] The 2008 JDRF landmark randomized clinical trial (RCT)[46] showed no overall glycemia benefit with CGM use in the younger age groups (8–14 years and 14–25 years), likely related to <50% sensor wear usage in these groups. A secondary analysis demonstrated benefits across all age groups when the sensor was used ≥6 days/week.[47] RCTs and meta-analyses conducted since 2010 utilizing newer generation rtCGM systems more consistently show that use of rtCGM is able to improve glycemia in both children and adults with T1D and, depending on the population studied, benefits are seen in terms of lower HbA1c concentrations, increased TIR, reduced hypoglycemia (including severe hypoglycemia), and reduced glucose variability.[3,43,48–52] There is now emerging evidence that improvement in glycemia is equivalent in users of insulin pump therapy and MDI therapy.[50,53–57]

Contemporary large registry-based studies have shown that compared to SMBG, use of rtCGM is associated with lower HbA1c levels, a higher proportion of people achieving ISPAD HbA1c targets, and fewer episodes of DKA in children and adolescents.[2,17,58–63] This positive effect on HbA1c has also been seen in a Swedish registry-based study that described a progressive decrease of HbA1c in very young children during the 2008–2018 period, in parallel with the increasing use of pumps and CGM.[64] Data from national population-based registries following rtCGM/isCGM reimbursement programs report improvement of T1D glycemic outcomes in children, adolescents, and adults.[65–67]

In contrast, registry-based studies have not consistently shown a lower number of severe hypoglycemic events in people using rtCGM.[2,60–62] Tauschmann et al. analyzed real world data from people with T1D aged <18 years from Germany, Austria, and Luxemburg in the DPV Registry and showed a reduction in severe hypoglycemic events during the first year of CGM use.[59] Interestingly, data from observational studies in children and adolescents, suggest that, irrespective of insulin delivery system, early initiation of CGM within 1 year of T1D diagnosis is associated with fewer severe hypoglycemic events and more favorable glucose outcomes.[68,69]

RCTs using the latest-generation non-adjunctive rtCGM systems have shown positive effects on both HbA1c levels and TIR[70,71] in adolescents and young adults. The MILLENIAL Study of a factory-calibrated rtCGM showed that TIR increased when compared with SMBG.[71] Supporting this finding, data from single-center observational studies with selected population aged <20 years have reported a decrease of HbA1c levels after initiation and with uninterrupted use of rtCGM.[68,72]

Data from RCTs in young children have replicated the results of studies from adolescents and young adults. Though data from small observational studies suggest that CGM can be used successfully in children <8 years,[73–75] a more recent trial of non-adjunctive rtCGM in 143 very young children (mean age 5.7 years) did not show a statistically significant improvement in TIR. However there was a substantial reduction in the rate of hypoglycemia seen with rtCGM vs traditional

capillary BG measurements over 6 months.[76] Using data from the Slovenian National Registry, Dovc et al demonstrated that the use of CGM was well tolerated by pre-school children and that a positive effect was observed in glucose variability.[75]

isCGM systems

To date very few RCTs have been conducted using isCGM,[55,77] and only one in adolescents and young adults.[77] The IMPACT multicenter isCGM RCT focused on ameliorating hypoglycemia and involved adults with HbA1c <7.5% at study entry. It demonstrated that isCGM use reduced time spent in hypoglycemia, reduced glucose variability, and improved TIR (3.9 to 10.0 mmol/L, 70 to 180 mg/dl) when compared to SMBG.[55] Similar results, including significantly reduced time in hypoglycemia without deterioration of HbA1c were observed in a subgroup analysis of the IMPACT RCT in adults with T1D managed with MDI therapy.[78] However, the effect of this technology in those with suboptimal glycemia remains less certain. In a 6-month RCT in youth aged 13 to 20 years with elevated HbA1c (HbA1c ≥ 9%), Boucher et al did not demonstrate differences in HbA1c levels when using isCGM compared to SMBG.[77] Nevertheless, this youth population increased testing frequency 2.5 fold and reported a higher satisfaction with its treatment.[79]

Data from observational clinical studies in children aged 4–18 years at isCGM initiation have shown greater TIR[80] and lower HbA1c[80,81] compared to SMBG use prior to isCGM start,[80,81] similar to what has been described in adults.[82–84] Interestingly, when comparing isCGM users across different age groups,[85,86] benefits were more pronounced in children under 12 years[85] and preschool children[86] compared to adolescents[85,86] and adults.[85] Scanning frequency (11–13 scans/per day) is associated with favorable glycemic markers (HbA1c and TIR) though not with reduction of time in hypoglycemia.[80,81,85,87,88] These studies were all performed using first-generation systems without alarms for impending hypo- and hyperglycemia. Studies using newer systems with optional real time alarms and improved accuracy are needed.

In addition, anonymized real-world data studies have also shown increased scanning frequency benefits time in hypoglycemia.[67,89,90] One observational study in children and adults using data from 12,256 individuals in the Scotland national diabetes registry found that isCGM initiation was associated with significant reductions in HbA1c with the greatest reductions in those with highest starting HbA1c values and children <13 years of age; DKA episodes were also decreased except in adolescents; among those at higher risk for severe hypoglycemia requiring hospitalization (SHH), a marked reduction in SHH event rates was also observed.[91] A prospective real-world cohort study after 1 year of nationwide reimbursement of isCGM in Belgium reported fewer severe hypoglycemia and DKA events with the use of isCGM.[66]

Rt CGM versus isCGM

In recent years, studies directly comparing rtCGM and isCGM systems have been published, including observational studies in children and adolescents[92] and adults with T1D,[93] and one RCT in adults.[94] All showed superiority of rtCGM over isCGM in terms of improved TIR and reduced percentage of time in hypoglycemia. However, the number of studies and the number of trial participants were limited, particularly in children and adolescents. Additionally, mainly older generation devices were used.

TABLE 3 Basic guidelines for starting CGM use

Before initiation
• Review device components and features
• Advocate for insurance coverage/reimbursement
• Support consistent options for CGM supply provision
• Provide access to customer service contact for technological support
• Ensure/arrange access to CGM data platforms
Device insertion and adherence
• Review sensor site selection, site rotation, signs, and symptoms of cutaneous/subcutaneous issues
• Review insertion techniques
• Offer supplementary adhesive products. These include:
○ Wipes: Skin tac IV prep, skin prep
○ Dressings and barriers: Tegaderm, IV-3000, Hypafix
○ External Wraps: Coban, Pre-Wrap
• Offer adjunctive adhesive removers, such as Unisolve or Detachol, or products one may have at home, like baby oil
• Review signs/symptoms of skin irritation/contact dermatitis
Calibration
• For sensors requiring calibrations, discuss frequency of calibrations and ideal times to calibrate
○ Consider pre-emptive calibration schedule. If calibrations are required every 12 h, encourage persons to calibrate three times a day (for example, prior to breakfast, dinner and bedtime)
○ Discuss calibrating when glucose is relatively stable (arrow shows glucose stable, no rapid change on sensor glucose graph)
Alerts and alarms
• Consider leaving alerts off initially to help avoid alarm fatigue.
• When incorporating alerts, personalize them and use wide thresholds at first (i.e. 70-250 mg/dL [3.9–13.9 mmol/L]). These can be adjusted over time.
○ For those with recurrent hypoglycemia, set low alert first.
○ For those with sub-optimal glycemia, consider setting high alert first.
• In the beginning, do not employ rate of change or predictive alerts. Consider how these additional alerts may be actionable moments prior to incorporating them. This will help prevent alarm fatigue.
• Rate of change alerts or predictive alerts might be turned on in situations where rapid changes in glucose levels are more likely than under normal everyday conditions (e.g. more physical activity, eating different types of foods).
Retrospective Review
• Encourage downloading, if required, to review data
• Encourage retrospective data review to inform insulin dose titrations
Real-time data
• As appropriate discuss non-adjunctive use of sensor data
• Review significance of sensor lag
• Review significance of trend arrows
• Consider recommendations on adjustments of insulin doses based on sensor glucose values and trend arrows[111,112]

CGM use from diabetes onset

Tight glycemia from diabetes onset has been shown to benefit long-term glycemic trajectories in individuals with T1D.[95] Early introduction of CGM among children with new onset diabetes was

associated with a 0.66% lower HbA1c at 12 months after diagnosis compared to those who did not start CGM.[68] Long-term improvement in HbA1c over a 7-year follow up period was seen when CGM was initiated in the first year after T1D diagnosis compared to no CGM use or when CGM initiation after the first year.[96]

Residual beta-cell preservation, often assessed by residual C-peptide secretion, has long been a goal of interventions for persons with new onset T1D to decrease risk of long-term diabetes related complications.[97–99] There are several ongoing studies investigating the benefit of more modern factory-calibrated CGM and hybrid closed loop systems in preserving beta-cell function in the new onset period. As the role of CGM and CGM-derived metrics in clinical trials as outcome parameters is being established,[100] CGM will be used increasingly to monitor glycemic trajectories in pharmacologic intervention studies on diabetes onset or prevention. There will also be a role for CGM in the monitoring of people at high risk of developing T1D following positive islet antibody screening.[101,102]

Practical considerations

Education

Initial and ongoing education and training in CGM use remains a keystone to optimizing CGM uptake and long-term use, as glycemic benefits are only observed if the device is worn consistently.[103] While many aspects of CGM use remain largely intuitive,[104] structured training of youth and parents/caregivers about CGM device components, insertion, skin care, and data interpretation is critical to assure safe and effective use of this technology.[103,105] Further, ongoing education and support are recognized as essential to overcome barriers to consistent CGM use and as technologies are continuously updated.[103,106] Follow-up training is also recommended to teach users how to analyze and interpret their glucose data.[107,108] In addition, psycho-educational support is helpful to set realistic expectations and to address individual education and training needs.[103]

Structured educational material and written healthcare plans to support CGM use should also be provided to caregivers of children with diabetes, including daycare providers, school nurses, teachers, babysitters, after-school program supervisors.[103,109,110] Table 2 provides an overview of the structured education aspects to consider at CGM initiation (Table 3).

Exercise

CGMs can be helpful in reducing glycemic excursions associated with exercise, which represent a challenge for youth and their parents/caregivers.[113] RtCGM has proven to be effective in both the prevention and early detection of exercise-induced hypoglycemia.[114]

Limited data exist on the efficacy of isCGM in maintaining optimal glycemia during exercise when compared to rtCGM. In a RCT in adults with T1D, the use of rtCGM was superior to isCGM in reducing hypoglycemia and improving TIR during exercise.[94]

The use of predictive hypoglycemia thresholds and rate-of-change in glucose alerts in rtCGM devices, allows prompt action to avoid glycemic fluctuations during and after exercise.[94,115,116] Also, the use of thresholds for lower glucose values allows the user to consider carbohydrate consumption with respect to the rate-of-change in glucose and the trend arrows.[115–118]

A recent position statement recommends different glycemic ranges before, during and after exercise according to the age group, the type of exercise, the risk for hypoglycemia and in accordance with the trend arrows.[117] However, these recommendations represent a general approach that needs to be personalized for the individual child and parents/caregivers.

CGM remote monitoring tools also offer the possibility for parents/caregivers to facilitate supportive action in case of glycemic excursions associated with exercise[118] or to avoid post-exercise nocturnal hypoglycemia in children.[119]

For more information on exercise in children and adolescents with diabetes, please refer to the ISPAD 2022 Consensus Guidelines Chapter 14 on Exercise in children and adolescents with diabetes.

CGM and skin issues

Inflammatory skin reactions elicited by non-specific skin irritation or delayed-type allergy to adhesive or device materials remain a barrier to consistent long-term CGM use, especially in young children.[120] Rate of cutaneous complications from CGM use in clinical trials were comparably low with one event per 8 weeks of sensor wear-time.[121] However, there appear to be discrepancies between trial reporting and observational data.[121] Reports on skin issues related to CGM use are becoming more frequent with the long-term use of sensors and the availability of devices with longer wear time.[122,123] CGM-associated skin conditions include localized eczematous reactions under the device or the fixation plasters, post inflammatory hyperpigmentation at CGM sensor insertion sites, device-associated pruritus at the application site.[124,125] Increasing evidence identifies sensitizing components of sensors and adhesives as factors possibly responsible for skin reactions, including allergic contact dermatitis.[126,127] The exact adhesive composition is rarely made available by manufacturers, but most devices contain acrylate, which can cause contact dermatitis.[127] Recently, initiatives for full and accurate labeling of the chemical composition of devices were presented.[128] Strategies to preserve skin integrity include correct device placement, prophylactic skin care, proper removal techniques, and promotion of skin healing. In addition, barrier agents to minimize the risk of hypersensitivity reactions may reduce the risk of skin irritation due to frequent sensor use.[129]

For more information on skin related issues, please refer to the ISPAD 2022 Consensus Guidelines Chapter 14 on Other complications and associated conditions in children and adolescents with type 1 diabetes.

Remote monitoring

Mobile phone-based CGM systems have the ability to transmit glucose data to the "cloud," and allow for digital remote monitoring, whereby parents/caregivers are able to view a person's CGM tracing and receive alerts on their own devices, such as smartphones, tablets, and smart watches. Remote monitoring of CGM has been reported to improve several psychosocial outcomes in parents of children with diabetes, including quality of life, reduced family stress, and improved parental sleep.[119,120,130] Parents may have increased comfort in leaving their children with other caregivers (e.g., daycare, school, babysitters, etc.), given their awareness of the child's glucose levels and well-being from afar with remote CGM monitoring.[120] Remote monitoring

of CGM data in the school setting may enable a collaborative approach to diabetes management between the student with diabetes, parents, and school personnel.[110]

Parental fear of hypoglycemia has been associated with suboptimal glycemia in children with diabetes, especially hypoglycemia during the night-time.[131] The ability to remotely monitor CGM data has been shown to prevent prolonged nocturnal hypoglycemia in youth with diabetes.[132] The peace of mind afforded by the ability to monitor CGM data remotely and receive real-time alerts for glucose excursions enables better parental sleep,[119,120,130] and possibly comfort with in-range glucose values to improve overall glycemia.

However, conflicts can also arise because of remote monitoring of CGM data.[120] For example, youth with diabetes may have the feeling of being "policed" by their loved one, resulting in feelings of frustration. On the other hand, remote caregivers might experience unnecessary panic in certain situations such as falsely low alerts due to compression. This highlights the need for constructive communication around diabetes management with clear expectations regarding when and how caregivers should intervene based on remote monitoring of glucose data and alerts received. This is particularly important in adolescents who may desire increasing autonomy in diabetes management but can still benefit from the support of their parents and other caregivers.

Telemedicine

CGM is a helpful tool for facilitating real-time data sharing via web-based software solutions in the context of telemedicine visits so that healthcare professionals have retrospective glucose data for review. This allows healthcare professionals to easily review and interpret glucose data to make recommendations on therapy adjustments during telemedicine consultations. To that end, CGM use has become fundamental to effective remote diabetes care delivery, as cloud-based data acquisition can support meaningful interactions between families and the diabetes team. The COVID-19 pandemic in early 2020 accelerated the widespread adoption of telemedicine and remote person engagement.[133] Pediatric diabetes centers were among those who rapidly expanded telemedicine services to facilitate person care.[134,135]

Many observational studies regarding the utility of CGM were conducted during the COVID-19 pandemic.[136] However, solid evidence demonstrating the benefit of utilizing CGM data via telemedicine in improving clinical outcomes in youth with diabetes are lacking, but it will likely remain an important tool well beyond the COVID-19 pandemic. To achieve the greatest benefit from CGM, persons with T1D and caregivers may need more frequent touchpoints via telemedicine with the diabetes care team to learn how to leverage its full potential.

Despite the widespread adoption of telemedicine for people with diabetes and one of its key elements, that is, remote availability of glucose data for simultaneous review by people with diabetes and their healthcare professionals, socio-economic factors, including poverty and limited access to diabetes technology pose major obstacles to realizing its successful application. ISPAD advocates for more availability and equal access to diabetes technology for all people with diabetes.

4 | QUALITY OF LIFE AND PERSON WITH DIABETES PERSPECTIVES ON USE OF CGM

Uptake and continuous use of diabetes devices and technologies are associated with psychosocial and family factors. Psychosocial factors are broadly defined as behavioral, emotional, and social variables that characterize an individual across both dimensions of promoting health (e.g., resilience) and having negative effects on health (e.g., depression). The focus on psychosocial factors in relation to diabetes device and technology use has grown out of the broader interest in understanding how these factors impact diabetes management and health outcomes. For example, it is well established that personal strength and resilience factors, along with positive family communication, are associated with optimal management and outcomes.[137–139] Likewise, psychosocial factors such as diabetes distress, depression, and family conflict are common in youth with diabetes and often lead to suboptimal management and outcomes.[140–143] Herein, the current understanding of the association between psychosocial factors and CGM use will be highlighted.

ISPAD guidelines on the psychosocial care of youth and the American Diabetes Association guidelines for the psychosocial care of people with diabetes[144,145] highlight that attending to the psychosocial needs of all youth and their families is critical. Please refer to ISPAD 2022 Consensus Guidelines Chapter 15 on Psychological care of children and adolescents with type 1 diabetes.

Similarly, when considering whether diabetes devices and technologies should be recommended or encouraged, understanding the psychosocial aspects of the user and family will help optimize a good fit for the device. The most evidence is available for insulin pumps and CGM. CGM is linked to optimal glycemic outcomes and many users report greater treatment satisfaction.[146,147] There are also recent reports of significant alleviation of diabetes distress, worries about hypoglycemia, and improved general well-being.[148,149] Further, there are benefits of using CGM early in the course of type of diabetes[150] and during the global pandemic.[151] Person-reported outcomes have become integral and accepted parts of randomized trials on CGM, and offer a broader view of the lived experience of using devices in T1D management.[70] While there are significant benefits of CGM use, there are also reports of heightened worries[152,153] among adolescents and young adults and many discontinue CGM for a variety of reasons including cost, too many alarms, concerns about accuracy, and discomfort wearing a device on one's body.[154] Thus, setting realistic expectations for potential users and their families and providing referrals for any psychosocial need that may serve as a barrier to optimal use, are indicated. In addition, the following recommendations are made when considering CGM use (and more broadly device and technology use) in diabetes care practices:

- Portray the use of diabetes devices and technologies as an option that can be a good fit for many youth and families; provide education and encourage youth and families to review vetted websites and device informational materials.
- Encourage uptake and refrain from having youth and families "earn" the right to use devices (i.e., the requirement to achieve a

certain hemoglobin HbA1c level before considering starting a device). If payers/insurance companies require logging or other documentation prior to device approval, convey that information as a specific requirement of the payor and not an expectation of the diabetes care practice.
- Conduct a brief assessment of expectations and barriers to uptake and use. Common barriers are cost (often noted by parents of youth, and the youth themselves,[155] wearing multiple devices, sensation of wearing a device on a changing and growing body, frequent alarms and maintenance of device.
- Problem solve with the youth and their family on ways to break down barriers. This may require referral to a psychological care provider to teach problem solving skills.[144]
- If psychosocial needs are reported or identified, refer to psychological care provider.[144]
- Support youth and families in initiating CGM use, interpreting and using the CGM data to optimize diabetes management and reduce diabetes burden.

Beyond CGM, the use of other devices and technologies provides additional advice for prescribers and supporters of diabetes devices For example, in a report of 284 potential users of closed loop in the US and UK,[156] three themes were identified as critical for uptake: developing trust in the system and degree of control of it; features of the closed loop systems; and concerns about the everyday barriers to adoption. Of note, children and adolescents differed from parents in that youth primarily identified needs specific to their immediate contexts (e.g., school and peers). Parents were most concerned about the accuracy and ensuring that systems stabilize glucose levels and reduce risk for long-term complications. Other reports emphasize these same ideas of setting realistic expectations[157,158] and potential benefits on quality of life and well-being are already being realized with closed-loop systems.[147,159,160] In the United States, the FDA recognized the first Medical Device Development Tool (MDDT) as the INSPIRE scales, a person reported outcome survey evaluating expectations and well-being related to device use.[161] This can be considered when formally evaluating programs for initiating and sustaining device use.

In sum, the current evidence base points to psychosocial and quality of life benefits from using CGM and other devices such as hybrid closed loop systems. Interventions to reduce barriers to technology use are actively being investigated.[154] However, more clinically-translatable research, specifically conducted in the pediatric population is needed on the best ways to break down barriers to device and technology use and prevent discontinuation. This likely rests in setting realistic expectations, teaching effective problem-solving skills (general and technology-specific), and viewing digital health applications as a scaffolding for youth to internalize the salience and routine of specific health behaviors.

5 | CONCLUSIONS

Over the past 30 years, glucose monitoring has evolved from urine glucose testing and fingerstick capillary BG measurements to continuous glucose monitoring systems using factory-calibrated interstitial sensor technology. Along with significant improvements in CGM technology (including accuracy, device size, prolonged sensor lifetime, and user-friendliness), wider availability of CGM systems due to better coverage by national and private insurance in more parts of the world and demonstrated benefits of their application compared to SMBG in T1D, CGM has become standard of care for people with T1D in many countries.

Today, CGM technology is at the heart of diabetes management. CGM specific metrics, in particular "TIR" (defined as percentage of time with sensor readings between 70 and 180 mg/dl, 3.9 and 10 mmol/L) have been adopted as useful clinical markers[162] and outcome measurements[100] that supersede or complement HbA1c for a wide range of people with diabetes (see ISPAD 2022 Consensus Guidelines Chapter on Glycemic Targets). Manual or automated upload of CGM data to cloud-based platforms enables sharing and remote reviewing of the data. This has been and will continue to be instrumental in providing telemedical care during the COVID-19 pandemic and beyond. Particularly noteworthy, significant progress has been made in CGM-enabled algorithm-driven automated insulin delivery (AID) delivery in the form of a hybrid artificial pancreas (see ISPAD 2022 Consensus Guidelines Chapter on Insulin Delivery).

With the advent of factory-calibrated CGM sensors licensed for non-adjuvant use, it seems as if SMBG has started to take a back seat in glucose monitoring. However, it still has an important role. Even users of AID systems with calibration-free non-adjuvant CGM still have to perform capillary BG measurements in certain situations, that is, if sensor readings and personal perception do not match, to confirm hypoglycemia, to do manual calibrations if sensor readings are not accurate, and when no CGM data are available.

Of course, people who do not have access to CGM will still rely on SMBG devices. CGM devices and sensors are expensive and may not be available in many countries. Insurance coverage may also be limited. Over time, these devices will continue to become more widely available and better coverage by both national and private insurance is anticipated. ISPAD advocates for increased availability of CGM for children, adolescents, and young adults with diabetes. Where available, CGM should be initiated in all children, adolescents, and young adults with T1D as soon as possible after diagnosis.

This chapter has reviewed evidence on glucose monitoring technology in children, adolescents, and young adults. Recommendations on their use and practical advice regarding their applications has been provided. Since this is a rapidly evolving area of research and practice, further innovations and updates are to be expected.

CONFLICT OF INTEREST

Martin Tauschman reports having received speaker honoraria from Eli Lilly, Medtronic, and NovoNordisk. Martin Tauschman has served on an advisory board of Abbott. Daniel J. DeSalvo has served as an independent consultant for Dexcom and Insulet. Lori M. Laffel is a consultant/advisor to Dexcom, Insulet, Medtronic, and Roche. Dmitry N. Latpev has received honoraria for participation on advisory boards for Abbott, Novo Nordisk, Sanofi, Eli Lilly, and LifeScan and as a speaker for

Abbott, LifeScan, Medtronic, Novo Nordisk, Sanofi, and Roche. Linda A. DiMeglio has consulted for Vertex, served on Mannkind, Merck, and Abata advisory boards, and received research support to her institution from Caladrius, Lilly, Mannkind, Medtronic, Provention, and Zealand All other authors have no relevant COI to report.

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How to cite this article: Tauschmann M, Forlenza G, Hood K, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Glucose monitoring. *Pediatr Diabetes*. 2022;23(8):1390-1405. doi:10.1111/pedi.13451

Received: 23 September 2022 | Accepted: 24 September 2022

DOI: 10.1111/pedi.13421

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery

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KEYWORDS: automated insulin delivery, connected pens, diabetes technology, insulin pumps

1 | WHAT IS NEW OR DIFFERENT?

In 2018, the inaugural guideline on diabetes technology was published. Like the technology used in daily life, the field of diabetes technology has seen rapid innovation and growth in the devices used for management. To review technologies more clearly, these guidelines have been divided into two parts: Diabetes Technologies: Glucose Monitoring and the present chapter, which focuses on insulin delivery methods.

Updates in insulin delivery include the advent of connected pens, which have created a means to utilize technology without requiring on body devices, though studies in the pediatric population remain sparse. Across a wide age spectrum, both clinical trials and real-world data have clearly demonstrated improvements in glycemia with use of automated insulin delivery (AID), especially overnight. Thus, the most advanced insulin delivery technology that is available, affordable, and appropriate for the individual should be offered, with the goal of personalized care. Use of insulin delivery devices requires special attention to psychosocial aspects of care as well as delivery of structured, yet tailored, education to create the foundation for success. These issues are covered in greater detail in this updated chapter.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | General principles for insulin delivery technology

- It is recommended that youth be offered the most advanced insulin delivery technology that is available, affordable, and appropriate for them. **B**

2.2 | Pens

- Connected insulin pens have the potential to improve diabetes management on intensive insulin therapy with multiple daily injections (MDI). **C**

- Connected pens if available may be offered to interested youth who prefer not to have an on-body device. **E**

2.3 | Pump therapy general principles

- Continuous subcutaneous insulin infusion (pump) therapy is recommended and appropriate for youth with diabetes, regardless of age. **A**
- Infusion set failures are common with any insulin pump therapy and must be recognized promptly to avoid diabetic ketoacidosis (DKA). **B**

2.3.1 | Not-integrated pumps

- Insulin pump therapy is safe and effective in youth with type 1 diabetes (T1D) to assist with achieving glycemic targets. **A**
- Insulin pump therapy reduces episodes of hypoglycemia. **B**
- Insulin pumps reduce chronic complications of T1D in youth, even when compared to those with similar hemoglobin A1C (HbA1c) levels on MDI therapy. **B**

2.3.2 | Sensor augmented pump (SAP)

- Sensor augmented pump (SAP) therapy is superior to MDI with self-monitoring of blood glucose (SMBG) in reducing HbA1c without an increase in hypoglycemia or severe hypoglycemia (SH). **A**
- Sensor use must be at least 60% to realize these benefits. **A**

2.3.3 | Low glucose suspend (LGS) system

- LGS systems reduce the severity and duration of hypoglycemia as compared to not integrated pump and SAP, without a deterioration in glycemia, as measured by HbA1c. **A**

2.3.4 | Predictive low glucose suspend (PLGS) system

- PLGS systems reduce frequency of and exposure to hypoglycemia. **A**
- Both LGS and PLGS systems do not lead to a rise in mean glucose levels, and lead to increased confidence and trust in the technology, more flexibility around mealtimes, and reduced diabetes distress for both people with diabetes and caregivers. **A**
- If AID systems are not available, PLGS is strongly recommended for all people with T1D to mitigate hypoglycemia; in cases of limited availability of more advanced technology, LGS is strongly recommended for all people with T1D to reduce the severity and duration of hypoglycemia. **A**

2.3.5 | AID system

- AID systems, also known as closed loop (CL), are strongly recommended for youth with diabetes. **A**
- AID systems improve time in range (TIR) by minimizing hypoglycemia and hyperglycemia. **A**
- AID systems are especially beneficial in attaining targeted glycemia in the overnight period. **A**
- If people with diabetes choose to use open-source automated insulin delivery systems, support from care providers is encouraged. **E**

2.4 | Behavioral, psychosocial, and educational considerations of insulin delivery devices

- It is strongly recommended that diabetes providers/educators implement a standardized training approach when new insulin delivery devices are integrated into care. **C**
  - For optimal outcomes, people with diabetes and their families should be advised to use the AID system as intended. **C**
- Counsel youth and their caregivers about realistic expectations for glycemic outcomes and the effort required for successful use of all insulin pump technologies. **B**. This is especially important in those with suboptimal glycemia, challenges with engagement with the current treatment plan, or higher burnout/mood concerns. **C**. Expectations include:
  - Glycemia will likely improve but will not always be at the desired target, and glucose fluctuations will still occur, especially after meals.
  - There will be an ongoing need for engagement in diabetes management behaviors (including engagement with the AID system), especially around mealtimes. People with diabetes should count carbohydrates and deliver meal boluses for most AID systems.
  - An adjustment period of approximately one month should be anticipated when transitioning to new devices.

3 | INTRODUCTION

Despite over 100 years of insulin therapy, glycemia remains suboptimal for many individuals living with diabetes. Data from international diabetes registries highlight that most youth with T1D do not meet the ISPAD targets for HbA1c.[1–6] Additionally, hypoglycemia and SH continue to plague youth with T1D.[7–10] While moderate fear of hypoglycemia may be beneficial, significant fear of hypoglycemia may prevent people with diabetes, and their caregivers, from attaining glycemic targets.[11] Yet, population-based studies show that reductions in HbA1c are not associated with increased risk of SH.[8,12] Importantly, use of diabetes technologies have been shown to improve glycemia.[5,13–18] Despite this, integration of diabetes technologies into the care of youth with diabetes remains variable and there are disparities in the care of youth from racial and ethnic minority

backgrounds and those of lower socioeconomic status.[19–24] A recent meta-analysis highlighted that most of the existing literature on pump therapy in youth with T1D reflects studies conducted in high-income countries; only 38% reported race/ethnicity of the population included and <25% of studies provided details regarding family socioeconomic status, parental occupation, and parental education/literacy.[25] Yet, a subanalysis of individuals from historically disadvantaged groups suggested that the use of diabetes technologies improved overall glycemia.[25]

While care has hitherto focused predominantly on achievement of consensus guideline targets for HbA1c, in recent years, there has been more widespread adoption of time in range (TIR) to guide clinical decision-making and define treatment goals.[26,27] See ISPAD 2022 Consensus Guidelines Chapter 8 on Glycemic targets and glucose monitoring in children, and adolescents with diabetes and Chapter 16 on Diabetes technologies: glucose monitoring. Studies demonstrate a correlation between TIR, defined as 3.9–10.0 mmol/L (70–180 mg/dl), and HbA1c concentration.[28–30] Also of central importance are metrics to assess disease management that extend beyond glycemia, particularly patient-reported outcomes.[27] These assessments are especially important as early advances in diabetes treatment may have inadvertently increased the burden of diabetes care, detracting from quality of life and psychosocial health.[31–34] Thus, a body of research has explored how the burdens of these technologies can be offset by the benefits they may provide, determining how to set realistic expectations for what assistance new therapies may provide, and methods to ensure transition to more advanced technology is associated with appropriate training on device use.

In 2018, ISPAD created the first consensus guidelines on Diabetes Technology.[35] However, with the rapidly evolving technology landscape, future iterations of these guidelines will be divided into two parts. Information on Insulin Delivery will be covered herein, and Glucose Monitoring with discussion of both capillary fingerstick glucose measurements and continuous glucose monitoring (CGM) will be presented in ISPAD 2022 Consensus Guidelines Chapter 16 on Diabetes technologies: glucose monitoring. These two chapters are intertwined, but the purpose of this chapter is to review insulin delivery technologies in children, adolescents, and young adults and to provide practical advice and approaches on their use. Topics include connected insulin pens, insulin pumps, SAP, LGS, PLGS, and AID, and culminates with behavioral, psychosocial, and educational considerations of insulin delivery devices.

4 | CONNECTED INSULIN PENS

Insulin pens continue to be a popular insulin delivery modality in young people with diabetes due to their ease of use and increased dosing accuracy compared to insulin delivery using vials and syringes. While the number of children utilizing insulin pump therapy continues to rise,[3] many children and adolescents do not wish to be tethered to a device and desire the less visible nature of MDI. Pen device technology has advanced significantly over the past 40 years, including the addition of a memory function in some pens. More recently, "smart" or connected insulin pens or pen cap devices that pair with smart phone applications and CGMs have been developed, allowing pen users access to benefits such as data collection, alerts and reminders, and dosing calculators that take insulin on board into account.

Data on the use of connected insulin pens in children are limited. A number of studies have reported high satisfaction and ease of use of pens with a memory function[36–39]; however, no significant improvement in glycemia has been noted when compared to use of insulin pens without a memory function.[40,41] One study noted that youth aged 2–18 years using the NovoPen ECHO device demonstrated increased rates of self-injection as compared to the mode of insulin delivery used prior to the study, which included conventional insulin pens or syringes.[41] Literature suggests Bluetooth-enabled pen cap device accurately detect insulin dosing and provide the person with diabetes and healthcare team with useful data, including assessing engagement with the prescribed regimen and the opportunity to optimize insulin doses through retrospective report review.[42–44]

A cost-effectiveness analysis based on adult data reported that connected pens could improve life expectancy compared to standard of care with a cost savings due to lowered frequency and delayed onset of complications.[45] Pediatric studies are needed to determine the impact connected pens will have on glycemic measures, including both TIR and HbA1c, as well as usability and satisfaction with these devices.

4.1 | Practical considerations for connected pens

"Smart" or connected pens eliminate the burden of dose calculation. Further, the insulin on board feature may reduce the risk of hypoglycemia from stacked correction doses that are given too frequently in response to hyperglycemia. Like pump therapy, success hinges on ensuring people with diabetes have the information necessary to program the dose calculator. Set up of the dose calculator requires the correction factor, target glucose, duration of insulin action, and insulin to carbohydrate ratios to be used. The calculator can also be programmed with different settings by time of day. Meal coverage with some connected pens allows for a simplified approach where the size of the meal (small, medium, large) is used to select a discrete insulin dose to be delivered. Long-acting insulin dose reminders, temperature tracking, and information about the units of insulin remaining in the pen can also aid with daily diabetes management. Currently, one system provides tracking of both rapid- and long-acting insulin doses with delivery of the dose recorded, but not the actual amount administered. Many connected pens allow for half-unit dosing increments, which can be especially helpful for young children. For youth with diabetes, who go back and forth between home and school settings, the ability to have more than one rapid-acting insulin pen paired can allow for one pen to be kept at school. Downloading device data obtained with these pens is essential to have the best success with dose optimizations.

5 | INSULIN PUMPS

Insulin pump therapy is recommended for all youth with T1D. This mode of insulin delivery has been found to be safe and effective for

children, adolescents, and adults. Additionally, insulin pump therapy is the foundational component of more advanced insulin delivery methods, which are discussed later in this chapter.

5.1 | The dawn of technology use in diabetes care

Insulin pump therapy was introduced in the late 1970s.[46–48] However, insulin pump therapy integration into the care of youth with T1D was minimal until the turn of the century. Since then, observational and cohort studies have shown pump use is associated with mean reductions in HbA1c of 0.2%–1.1%[49–62] and decreases in clinically-important hypoglycemia[49–54,57–63] without associated increases in BMI.[49,51–62] These data hold true regardless of whether the MDI comparator group used NPH[49–58,61,64] or glargine insulin.[65–68] Yet, randomized controlled trials (RCTs) assessing insulin pump use have yielded conflicting results, with some showing improvement of glycemia with use of the technology.[65,66] Even in RCTs where no lowering of HbA1c was observed, continued use of the devices after the end of the study,[69–71] higher reports of treatment satisfaction,[72] and decreased diabetes-related worry highlight that benefits extend beyond glycemic metrics.[73] Interestingly, a prospective examination of nearly 1000 youth on either pump or MDI therapy found lower rates of retinopathy and peripheral nerve abnormality in the insulin pump-treated group despite similar HbA1c.[74] Meta-analyses have shown reductions in mean HbA1c[75–77] and decreased rates of SH[77] with pump therapy as well as a reduction of total daily insulin dose with pump use.[75,76]

Given that people recruited into RCTs generally do not reflect the general population of children with T1D, real-world registries provide important data regarding the benefits of pump use. In a cross-sectional comparison of three large, transatlantic registries, which included the U.S. based Type 1 Diabetes Exchange clinic registry (T1DX), the German/Austrian Prospective Diabetes Follow-up Registry (DPV), and the English/Welsh National Paediatric Diabetes Audit (NPDA), a pooled analysis of nearly 55,000 pediatric participants showed that pump use was associated with lower mean HbA1c (pump 8.0 ± 1.2% vs injection: 8.5 ± 1.7%, $p < 0.001$).[15] The T1DX and DPV registry have both demonstrated increased pediatric use of pump therapy over time.[3,78] The SWEET (Better control in Pediatric and Adolescent Diabete**S: W**orking to cr**E**ate C**E**n**T**ers of Reference) centers found that almost half of the 16,000 registry participants used pumps, and this technology was associated with lower HbA1c and lower daily insulin dose as compared to MDI.[79] More recent data have corroborated this finding.[17,18] The long-term benefits of pump therapy have been demonstrated with sustained improvement in glycemia.[63,80,81] Further, registry data have also shown pump therapy is associated with lower rates of SH and DKA.[9,81–83]

TABLE 1 Indications for use of insulin pumps in pediatrics—adapted from Reference 84

Insulin pumps are recommended for all youth with diabetes. Specific factors that support the recommendation for insulin pump therapy include:

- Recurrent severe hypoglycemia
- Wide fluctuations in glucose levels regardless of HbA1c
- Suboptimal diabetes control (i.e., HbA1c exceeds target of 7.0% or TIR is <70%)
- Microvascular complications and/or risk factors for macrovascular complications
- Targeted metabolic control but insulin regimen that compromises lifestyle
- Young children and especially infants and neonates
- Children and adolescents with pronounced dawn phenomenon
- Children with needle phobia
- Pregnant adolescents, ideally preconception
- Ketosis prone individuals
- Competitive athletes

Contraindications to pump therapy:

- Preference of the person with diabetes not to use technology[a]
- Significant skin irritation/allergy making pump/sensor wear difficult[b]

[a]Providers should still provide information on technologies at each follow up visit to assess if there is a desire to change mode of insulin delivery.
[b]Consider referral to dermatology to aid with overcome issues with skin irritation.

T1D is recommended to be on pump therapy.[84] Indeed, as evidenced by the accumulated data presented above, standard insulin pump therapy is recommended for all youth with diabetes if access to more advanced diabetes technologies, including sensor augmented pump therapy (SAP), LGS, PLGS, and AID (described fully later in this chapter), is limited. Further, the ISPAD 2022 Consensus Guidelines Chapter 23 on Managing Diabetes in Preschoolers states pump therapy is the recommended mode of insulin delivery for those under the age of 7 years.[85] While concern is sometimes expressed over how daycare providers/school personnel will adopt this technology, one study suggests that children whose parents work outside of the home tended to see the largest improvement in glycemia with transition to pump therapy.[62]

Data demonstrate that pump therapy can be successfully used in children who have suboptimal glycemia prior to the transition to this mode of insulin delivery. In a study of 125 youth, those with the highest HbA1c levels (>9.0%) showed the largest decrement in HbA1c once pump therapy was initiated.[86] Immediate incorporation of pump therapy from the time of diagnosis has been shown to be successful in terms of achievement of glycemic targets.[87–90] While it has been postulated that achieving more targeted glycemia shortly after diagnosis may preserve beta cell function, this has not yet been substantiated.[89,91]

5.2 | Incorporation of pump therapy regardless of age, HbA1c or disease duration and clinical follow up

In 2007, a consensus guideline on use of pump therapy in youth with T1D (adapted in Table 1) provides solid evidence that every child with

5.3 | Barriers to adoption of pump therapy and predictors of success

Universal adoption of insulin delivery technologies has not occurred, with wide variation in implementation among centers, even those with similar

populations.[92] A Pediatric Diabetes Consortium study of 8 US clinical centers demonstrated frequency of pump use within the first year after diagnosis ranged from 18% to 59% of participants.[93] Initiation of pump therapy within a year was more common in those with private health insurance, annual family income over $100,000, a parent with a college education, and in non-Hispanic White individuals.[93] A T1DX study also reported widely variable pump use among centers and concluded health-care provider preferences influence the proportion of people using pumps in a given center.[94] Consistent findings of inequities in pump and CGM use in those of lower socioeconomic status and racial disparities with integration of these technologies have also been described in the literature.[19–24] Further potential barriers to uptake of the technology voiced by those with diabetes have included concerns regarding the physical footprint and interference of the device, therapeutic effectiveness of the technology and, to a lesser extent, financial burdens this mode of insulin delivery may cause.[95] In some countries, non-coverage, or incomplete coverage of pump therapy by the health care/insurance system likely influences the low adoption rates of this technology.[15,92]

5.4 | Frequency and causes of discontinuation of pump therapy

Pump therapy discontinuation is uncommon. Over the period of 1995–2009, the DPV registry found low attrition at 4%.[96] Adolescents aged 10–15 years had the highest rate of pump discontinuation, and those who discontinued were more likely to be female.[96] Similar results were noted in a T1DX registry analysis.[97] Reasons for discontinuing pump therapy included problems with wearability (57%), disliking the pump or feeling anxious (44%), and problems with glycemic control (30%).[97] Higher depressive symptoms, as captured by the Children's Depression Inventory, have also been reported to precede cessation of pump use.[98] Those who started on pump therapy and discontinued this mode of insulin delivery ($n = 9$) were predominately female and mean depressive symptom scores were reduced with the transition to MDI therapy.[98] To identify what might facilitate resumption of this technology, data collected via self-report for those >13 years old and via parental response for children aged 6–<13 showed improvements in infusion catheters, integration of blood glucose levels directly into the pump, and advances in some technical aspects of the pump, including reduced size of devices, water-resistant devices, and a reduction in emitted noise, would be motivating factors.[97]

5.5 | Complications of pump therapy: infusion sets and hypertrophy

Insulin pump-related adverse events are common and include infusion set failures, pump malfunctions, alarms, and other problems, with 40% to 68% of pump users experiencing such events.[99–103] Questions remain regarding whether steel cannulas or flexible Teflon catheters are ideal and whether certain infusions sets are better based on the age of the person using the pump or individual body habitus. As steel cannulas are less likely to kink or dislodge, they may be the ideal infusion set for the youngest children. The major concern is full or partial occlusion or dislodgement of the site thereby interrupting the insulin delivery and putting the user at risk for developing ketoacidosis. Strategies for failed infusion set detection continue to be explored and include fault detection algorithms, whereby the sensor glucose levels and amount of insulin delivered by the system are used to help detect or predict an infusion set failure,[104,105] and more recently the feasibility of using subcutaneous continuous ketone monitors.[106]

Some studies have documented between a 2 to 5-fold higher risk of DKA in those on pump therapy.[107,108] Education on the risk of DKA and how to manage persistent hyperglycemia is the cornerstone to avoiding these issues. Mild DKA can often be quickly ameliorated by administering additional insulin with either a syringe or pen as soon as hyperglycemia and hyperketonemia/ketonuria occur.[109] See ISPAD 2022 Consensus Guidelines Chapter 13 on Diabetic ketoacidosis and hyperglycemic hyperosmolar state. For more details. Some have explored the concomitant use of a small dose of basal insulin, like glargine, to help minimize the likelihood of this complication.[110]

Lipohypertrophy, or local fat accumulation, at the site of insulin administration, is another frequently encountered issue with pump therapy.[111] Lipoatrophy, fat loss at the site of prior insulin infusion sites, is less common and has been seen more frequently in those with concomitant multiple autoimmune diseases.[112] Both conditions are categorized as lipodystrophy. A cross-sectional study of children and adolescents with T1D demonstrated a greater risk of these issues in those with higher insulin autoantibodies.[113] Lipodystrophy can impact how insulin is absorbed and thus lead to deterioration in glycemia. To avoid lipohypertrophy, it is recommended that infusion set placement be rotated. Once detected, placement of infusion sets should avoid the affected area to allow the tissue to heal, which often takes several months. See ISPAD 2022 Consensus Guidelines Chapter 19 on Other complications and associated conditions in children and adolescents with type 1 diabetes. Interestingly, placement of a CGM sensor in an area of lipohypertrophy was found not to impact sensor accuracy.[114] Thus, while the abnormal tissue is not being using for insulin infusion, the area of lipohypertrophy may continue to be used for sensor placement.

Finally, with repeated exposure to adhesives from medical devices, skin irritation is often noted. In one study where comprehensive dermatological examinations were done, localized eczematous reactions at the site of infusion cannula insertion were noted in 14% of youth,[115] and a survey of 143 youth documented that nearly half of the cohort reported non-specific eczema.[116] For more information on skin related issues, please refer to ISPAD 2022 Consensus Guidelines Chapter 19 on Other complications and associated conditions in children and adolescents with type 1 diabetes.

5.6 | Practical considerations with pump therapy

As pump therapy is the basis for other advanced insulin delivery technologies, the benefits and issues mentioned above may also apply to the technologies discussed in the next sections.

5.6.1 | Provider training

Clinicians need to be trained on devices to be competent and feel comfortable with offering diabetes technology. Yet, a survey of pediatric endocrinology fellows in the United States and Canada found that only 14.7% had formal training on pump and CGM.[117] A subsequent study of pediatric endocrine fellows ($n = 64$) in North America employed case-based vignettes with 20 multiple choice questions on either CGM or pump therapy delivered either via email or a mobile app.[118] Both curricula were effective in increasing the pre- to post-test assessment of knowledge base and participants found this method of education engaging.[118] This suggests potential for providers to be trained on these technologies through user-driven online learning modules. Without keeping abreast of technological advances, clinicians may inadvertently hinder device adoption and their optimal use.

5.6.2 | Educational materials

To help inform families of various insulin delivery modalities, simplified guides regarding options can be helpful to supplement in clinic conversations. One such resource is The Simple Guides (https://www.uscdiabetes.com/simple-guides), which is free to use and available in both English and Spanish. Another is available in French (https://www.ajd-diabete.fr/le-diabete/tout-savoir-sur-le-diabete/la-pompe-a-insuline/).

When preparing to transition from MDI to insulin pump therapy, one of the first steps is to have the person with diabetes, and their family, select the pump model they would like to use if insurance coverage or regional availability does not dictate a decision. To accomplish this, charts and literature describing the differences among models are helpful; online resources include the American Diabetes Association's consumer guide (https://consumerguide.diabetes.org), Diabetes Wise (https://diabeteswise.org), or the Panther Program (https://pantherprogram.org). Pump selection should be based on features desired by the person with diabetes, and their family, with guidance provided by the clinical team members. In some health systems, people with diabetes may not have a choice of systems.

5.6.3 | Initiating pump therapy

Generally, initial pump settings should be derived from the individual's total daily insulin dose. Table 2 provides some suggestions to determine initial pump settings. At the time of pump start it is also critical to advise families on associated risks, particularly that of potential infusion set failure and consequent metabolic decompensation. A useful framework for optimizing the transition is presented by Deiss et al.[124] For very young children or those with minimal insulin requirements, diluted insulin can be used to accurately deliver very small amounts of insulin.[125–128] See ISPAD 2022 Consensus Guidelines Chapter 23 on Managing Diabetes in Preschoolers and Chapter 9 on Insulin treatment in children and adolescents with diabetes for further details.

TABLE 2 Basic guidelines for starting insulin pump therapy

Total daily dose (TDD) prior to pump initiation
- Generally used to determine initial pump settings
- Consider reducing total daily dose at initiation in those at glycemic target or in youth with diabetes who have frequent or severe hypoglycemia.

Proportion basal versus bolus insulin delivery
- In older children and adolescents expect a 50/50 split
- In children <7 years, basal insulin delivery may be ~30%–35% of the TDD[119]

Determination of basal rates
- Take the amount to be delivered as basal (i.e., 50% of the TDD) and divide by 24 for the number of hours in a day (e.g., if daily basal insulin will be 20 units then hourly rate would be set at 0.8 units/h)
- Pre-school aged children may have higher basal insulin requirements between 9 p.m. and 12 a.m. and lower basal rates during early morning hours before breakfast[120]
- Adolescents may need increases in basal rates in the early morning to counter the dawn phenomenon[120,121]

Determination of correction factors/Insulin sensitivity factors
- If using correction factors prior to transition to the pump, start with the usual factors.
- Otherwise, a correction factor can be determined by dividing 1800 by the TDD if glucose values are in mg/dl (or by dividing 100 by the TDD if glucose values are in mmol/L). Depending on insulin sensitivity, the 1800 rule can be adjusted upward (2000/TDD) for those who are insulin sensitive or downward (1500/TDD) for those who are more insulin resistant.

Determination of insulin to carbohydrate ratios
- If using carbohydrate ratios prior to transition to the pump, start with the usual factors.
- Otherwise, carbohydrate ratio can be determined by dividing 500 by the TDD
- Young children may need more aggressive meal coverage and a 350 rule may be employed[122,123]

Close monitoring following initiation
- Use sensor glucose data with attention to pre-meal and 2-h post meal values to inform insulin dose titrations. For those using fingerstick blood glucose values, test blood glucose both pre- and 2-h post meal to guide dose titrations.
- Use overnight sensor glucose values to assess overnight basal rates. For those using SMBG, consider overnight checks at midnight and 3 a.m. to assess overnight basal rates

Optimal engagement with pump therapy includes
- Bolusing for carbohydrate intake, ideally prior to eating
- Understanding of how to treat hypoglycemia[a] → 10–15 g of rapid-acting carbohydrates should be given orally. This may need to be lowered to 5–10 g for those on LGS, PLGS, or AID systems
- Changing the infusion set at least every 3 days
- Continuous CGM use will allow for optimal performance for systems that integrate sensor glucose data to alter insulin delivery (i.e., LGS, PLGS, and AID)

[a]See ISPAD 2022 Consensus Guidelines Chapter 11 on Management of Hypoglycemia in Children and Adolescents with Diabetes.

Various factors have been associated with successful pump therapy. These include having more pre-programmed basal rates (correlated with lower HbA1c levels)[129]; the total number of boluses delivered daily correlates with HbA1c achieved; and basal insulin delivery accounting for <50% of the total daily dose. It is critical to encourage people with diabetes and their families to be engaged with

care.[130,131] Reviewing the importance of meal announcements should be emphasized at each follow up visit.

5.6.4 | Advanced pump features

More advanced features of pump therapy include the ability to set temporary basal rates that adjust the usually programmed basal rate for unique day-to-day variations in insulin sensitivity. This includes decreasing delivery for physical activity or increasing doses for situations like inter-current illness.[119] Temporary basal rates, including complete suspension of basal insulin delivery can help mitigate hypoglycemia associated with exercise.[132] Similarly, different pre-programmed basal patterns can be utilized for predictable times of differing insulin sensitivity, for example during menstruation in women.

Boluses of insulin can also be delivered in different manners to accommodate differences in food composition: (1) immediately, as a standard or normal bolus, (2) slowly over a certain duration of time, an extended or square bolus, or (3) a combination of the two, that is, a combo or dual wave bolus.[119] Boluses for high fat foods might be best handled as extended or combo boluses as the rise in blood glucose levels following the meal will be delayed by fat. For the extended bolus, the user sets the duration of the extension; whereas, for combo boluses the user not only chooses the duration to extend but also the amount to be delivered upfront (e.g., 40% of the bolus immediately and the remaining 60% over 4 h). Pumps can also reduce bolus insulin delivery based on the proportion of insulin that is still "active" from the last bolus, which may decrease the likelihood of post-bolus severe hypoglycemia.

5.6.5 | Reviewing data to optimize management

As insulin pump data can be uploaded or, more recently, are available through cloud-enabled sharing, clinic visits can be more productive with the wealth of data afforded. In addition to determining if insulin pump settings need to be optimized, these reports serve as the basis for clinicians to initiate a conversation on engagement with care. With information on the number of boluses per day or the average amount of carbohydrates entered per day, more structured instruction on meal bolusing is possible. Further, records regarding the frequency of infusion set changes helps providers broach the conversation on recommendations regarding infusion set changes and the importance of rotating sites. For more information on care delivery, see ISPAD 2022 Consensus Guidelines Chapter 7 on The delivery of ambulatory diabetes care to children and adolescents with diabetes.

6 | SENSOR AUGMENTED PUMP THERAPY

Sensor Augmented pump (SAP) therapy is defined as the combination or augmentation of a conventional insulin pump with CGM (Figure 1). For more details on CGM, please see ISPAD 2022 Consensus Guidelines Chapter 16 on Diabetes technologies: glucose monitoring. With CGM values viewed either on a separate reader or smartphone or through direct integration of sensor glucose values on the insulin pump, SAP therapy provides the data that a person with diabetes can choose to act upon instead of relying on fingerstick glucose measurements at specific time points. For example, if a sensor glucose value reaches a high alert threshold, a correction bolus can be delivered. Thus, while SAP does not allow for automation of insulin dosing, it provides the framework on which integrated systems are built.

6.1 | A single platform: The beginnings of SAP therapy

The first 6 month RCT comparing SAP to insulin pump therapy conducted in 12–72 year old participants showed similar reductions in HbA1c, but this was associated with significantly increased hypoglycemia exposure in those randomized to the insulin pump with SMBG group.[133] For those in the SAP group, sensor utilization more than 60% of the time was associated with HbA1c reduction.[133]

The Sensor-Augmented Pump Therapy for A1c Reduction (STAR) 3 study compared SAP with MDI and SMBG checks over a 1-year study period in device naïve participants with T1D, including 74 adolescents (age 13–18) and 82 children (aged 7–12).[134–136] The SAP group had a sustained greater reduction in HbA1c, less time in hyperglycemia, and reduced glucose variability.[136] Rates of SH and DKA were relatively low and did not differ between groups. Importantly target achievement was directly linked to sensor wear duration and was more prominent in the children's cohort (aged 7–12 years) who had sensor use that was 1.5 times higher than adolescents (aged 13–18 years).[136] The crucial impact of regular sensor use has been echoed in other trials.[137] Recent data demonstrate every 10% increase in sensor use frequency is associated with a 1.1% increase in TIR and a 1.0% decrease in TAR >10 mmol/L (180 mg/dl).[138]

Although SAP is more expensive than conventional insulin pump therapy, the additional clinical benefits and quality-adjusted life years they afford provide justification for considering this treatment a good value for the money spent, provided sensor use is persistent.[139,140]

SAP generates a wealth of information upon which insulin doses can be optimized. Yet, glycemic improvement relies on the user or a caregiver responding to the sensor glucose data to adjust insulin or other aspects of care. Classically, this has been done with the assistance of a health care provider; however, more recently automated algorithms to adjust pump settings have been employed. ADVICE4U was a RCT assessing the use of automated artificial intelligence-based decision support system that showed non-inferiority of the decision support tool when compared to provider-driven insulin dose titrations in a cohort of 108 participants aged 10–21 years.[141]

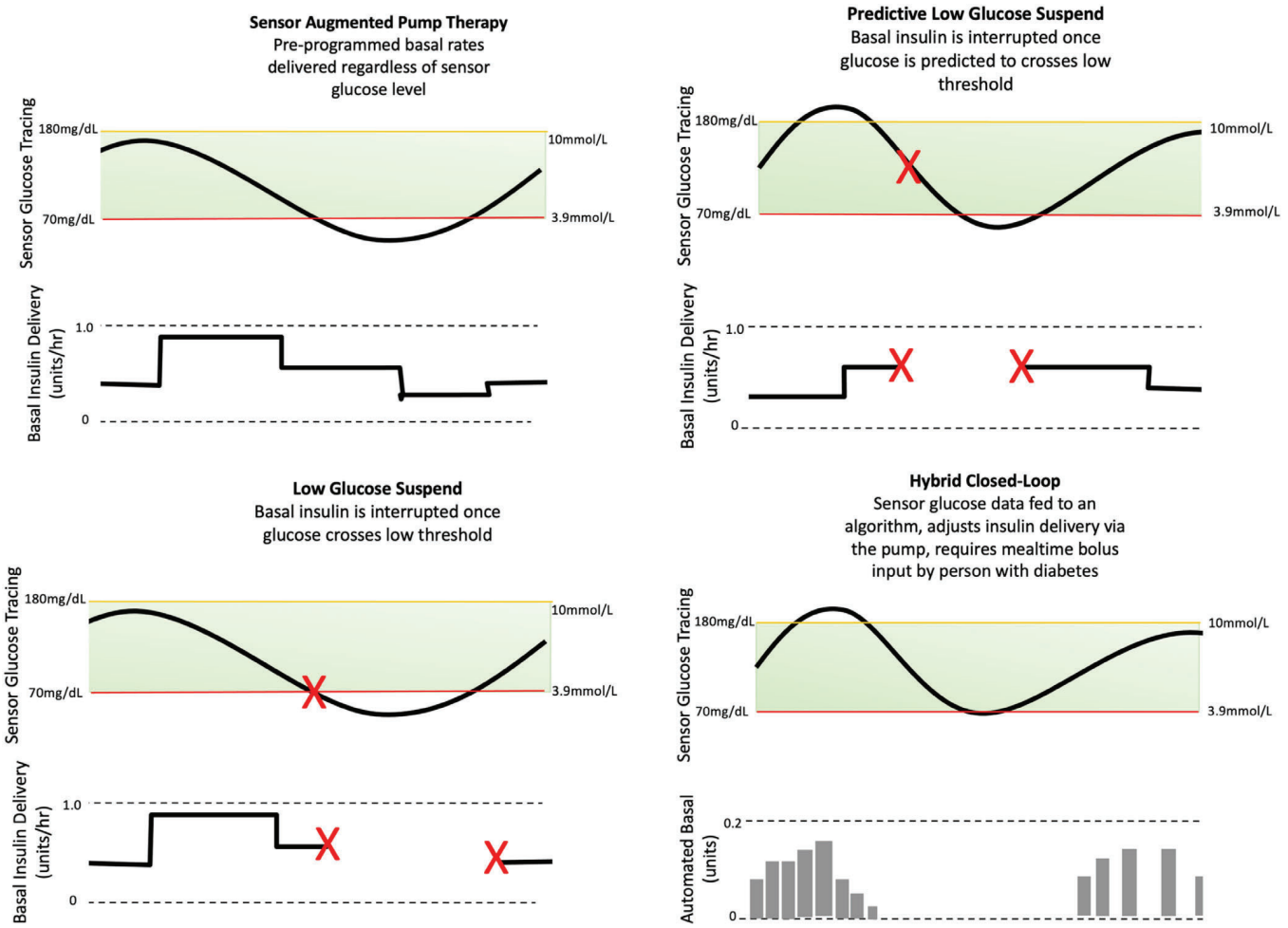

FIGURE 1 The evolution of insulin delivery technologies used in clinical care. Sensor glucose tracings are represented in black with time in target range 3.9–10 mmol/L (70–180 mg/d) represented in green. Discrete basal insulin delivery in units/h is noted in the bottom panel for each technology, except for hybrid closed loop where there is automated basal insulin delivery represented with the gray spikes. Red Xs mark both the glucose level when insulin suspension occurs as well as the start and stop of the suspension period on the basal insulin delivery graphs

7 | LGS SYSTEMS

7.1 | Reducing the severity and duration of hypoglycemia

With CGM data integrated into an algorithm on an insulin pump, altering insulin delivery based on sensor glucose readings is possible. The LGS system can suspend insulin delivery when the sensor glucose reaches a programmed low threshold (Figure 1). The insulin pump suspension lasts for 2 h in the absence of user intervention although the pump can be manually restarted at any time. The LGS feature is optional, and the pump functions normally if the feature is switched off, if sensor glucose data are not available, or if the sensor glucose value is above the predetermined threshold value.[142,143] Feasibility data on the efficacy and safety of LGS from early closed loop studies demonstrated that insulin suspension mitigated hypoglycemia risk.[135,144] LGS systems reduce risk of hypoglycemia, which may facilitate user engagement with bolusing.

LGS system benefits were first demonstrated in the real-world setting through the **A**utomation to **S**imulate **P**ancreatic **I**nsulin **R**esponse (ASPIRE) in-home study that enrolled participants with T1D aged 16–70 years. Sensor readings of <3.9 mmol/L (<70 mg/dl), <3.3 mmol/L (60 mg/dl), and <2.8 mmol/L (50 mg/dl) were significantly reduced without any deterioration in glycemia as measured by HbA1c with use of the LGS system.[145] Additionally, glucose levels remained stable even 2 h post nocturnal insulin suspension.[145] Another RCT that included younger people with T1D (mean age of pump users was 19.7 years vs 17.4 years in the LGS group) who had impaired hypoglycemia awareness also showed that LGS reduced the rate of severe and moderate hypoglycemia.[146] While the control group using insulin pumps and SMBG had 6 SH events, the LGS arm had none.[146] Nocturnal hypoglycemia was reduced without increases in HbA1c or episodes of DKA.[146] Real world observational studies leveraging data uploaded to CareLink, where age was self-reported and more than half of the participants were <15 years old, have substantiated the RCT findings showing benefits of LGS over SAP.[147]

The possible risk of hyperglycemia or DKA occurring due to insulin suspension in response to inaccurate sensor readings had been a concern prior to approval of LGS devices. This concern was addressed in a study that suspended insulin for 2 h overnight in a preprogrammed fashion for people at home, provided that pre-bedtime blood glucose was <16.7 mmol/L (300 mg/dl) and beta hydroxybutyrate was <0.5 mmol/L.[148] A total of 118 suspend nights and 131 non-suspend nights were included.[148] There was wide variation in the fasting blood glucose, but the mean fasting glucose levels on suspend nights was only 2.8 mmol/L (50 mg/dl) higher than non-suspend nights. Blood beta hydroxybutyrate levels were slightly higher in the morning after suspension of insulin but the difference was not statistically significant.[148] This suggests that LGS is safe even in the face of potentially inaccurate sensor glucose readings.[148]

While more advanced insulin pump therapies are now available and include PLGS and AID systems described below, one should be aware that advanced pumps are not available in all countries and may not be covered by certain health/insurance plans. In such circumstances, where LGS insulin pumps are available this insulin delivery modality is strongly recommended over other types of pumps. Studies have shown that LGS is cost-effective and should be particularly considered where there is a high risk of hypoglycemia, impaired hypoglycemia awareness or fear of hypoglycemia, which may lead to difficulty with achievement of glycemic targets.[149–151]

8 | PLGS SYSTEMS

8.1 | Mitigating hypoglycemia: the benefits of predictive low glucose suspend

PLGS systems interrupt basal insulin delivery to prevent hypoglycemia (Figure 1). Different systems are available; however, not all provide published evidence for successful use and therefore only systems with published peer reviewed data are recommended for use.[152] Early prototype PLGS systems requiring a bedside laptop showed the benefits of predictive insulin interruptions[153–155] and highlighted the safety of a PLGS system, as frequency of morning ketosis, defined as BHB >0.6 mmol/L, was not different between the PLGS and SAP.[156,157] This supports that there is no need for daily assessment of ketones for people using PLGS systems. Instead, ketones should be measured when glucose is persistently elevated or in the setting of illness, which is the same advice given to anyone on pump therapy.

The MiniMed™ 640G, 670G, 770G, and 780G systems (Medtronic, Northridge, CA) all offer the PLGS, which in these systems interrupts insulin delivery if the sensor glucose is predicted to reach 1.1 mmol/L (20 mg/dl) above the pre-set low glucose limit within 30 minutes. The system automatically resumes basal insulin delivery after recovery from hypoglycemia, with suspension duration ranging from a minimum of 30 minutes to a maximum of 120 minutes. Under experimentally-induced hypoglycemia through increased basal rates in an in-clinic setting, the system avoided hypoglycemia most of the time.[158] Two RCTs have been conducted with this system: one study ($n = 100$) showed a reduction in hypoglycemia events with PLGS use, but this group had a concomitant rise in the time spent in the hyperglycemia range, while the other trial ($n = 154$) showed a reduction in time spent <3.5 mmol/L (<63 mg/dl), with no deterioration in glycemia, as measured by HbA1c, in the PLGS group.[159,160]

Using data uploaded to CareLink, a real-world assessment of children <15 years, demonstrated that those on PLGS spent less time per day with sensor glucose in level 1 [<3.9 mmol/L (<70 mg/dl)] and level 2 hypoglycemia [<3.0 mmol/L (<54 mg/dl)] when compared to those on either SAP or LGS.[146] A subset of participants who switched from SAP to PLGS decreased monthly rate of sensor hypoglycemic events <3 mmol/L (<54 mg/dl) and <3.9 mmol/L (<70 mg/dl) by 49% and 32%, respectively.[147]

The Tandem t:slimX2 insulin pump with Basal IQ™ Technology (Tandem, San Diego, CA), is another PLGS which integrates the Dexcom sensor. While the suspension threshold is fixed to 4.4 mmol/L (80 mg/dl), the minimal duration of interruption is 5 minutes and insulin delivery will resume after any rise of sensor glucose values. A RCT of this system found that PLGS use led to a 31% reduction in sensor time <3.9 mmol/L (<70 mg/dl).[161] Real world registry data from adults using the Tandem systems show a significant reduction in time below range after PLGS start[162] and a 45% risk reduction for sensor time <3.9 mmol/L (<70 mg/dl) with no change in mean glucose.[163] After starting on the system, adults with T1D/caregivers of minors reported more device satisfaction and less diabetes impact on life with these findings sustained over 6-months of follow up.[164]

A meta-analysis including data on 493 children in 5 RCTs concluded that there is high quality evidence that PLGS is superior to SAP in decreasing time spent in hypoglycemia and nocturnal hypoglycemia.[152] This was accomplished without increasing percentage of time spent in hyperglycemia or episodes of DKA.[152] Another meta-analysis concluded use of PLGS during the overnight period was associated with an 8.8% lower risk of hypoglycemia when compared with non-PLGS overnight.[165]

8.2 | Practical considerations for SAP, LGS, and PLGS

Critical to the integration of SAP, LGS, and PLGS is successful adoption of sensor therapy. For evidence on sensor therapy, please refer to the ISPAD 2022 Consensus Guidelines Chapter 16 on Diabetes technologies: glucose monitoring. Topics that should be considered when initiating these therapies may include expected frequency of sensor use, and how treatment may vary when breaks from sensor therapy may occur.[166] This may be especially important in those utilizing systems that suspend insulin delivery as behavioral changes may be needed to mitigate the risk of hypoglycemia when the system is not being used.

With both LGS and PLGS system, alarms can be set for when pump suspensions occur. Yet, the usefulness of these alarms should be considered. For example, with PLGS systems that are designed to mitigate hypoglycemia, an insulin suspension alert would not indicate

the need for user intervention and thus it could be viewed as disruptive or burdensome to the person with diabetes. Instead, setting actionable alerts and alarms is critical, like setting a low alert threshold so rapid-acting carbohydrates can be used to treat hypoglycemia. Furthermore, with LGS systems people with diabetes should be encouraged to allow the system to work overnight, but if an alert occurs during the day they should consume carbohydrates and resume basal insulin delivery. With a PLGS system, should a hypoglycemic event occur despite insulin suspension, carbohydrate intake may need to be decreased to 5–10 g as compared to usual treatment strategies to prevent rebound hyperglycemia. Access to data from diabetes devices is essential to providers; these reports allow for more refined analyses, which can be used to determine insulin suspension frequency and whether changes in insulin doses and/or treatment for hypoglycemia are required.

9 | AID

AID systems, also referred to as closed loop (CL) or artificial pancreas systems, adjust insulin delivery in response to sensor glucose data. AID is safe and effective at reducing HbA1c and increasing TIR in children and is strongly recommended. With AID use quality of life improvements have also been noted in children with diabetes and their caregivers.

9.1 | AID approaches

AID systems consist of three components: an insulin pump, a CGM sensor, and an algorithm that determines insulin delivery. Several algorithms have been widely tested: proportional integrative derivative (PID),[167,168] model predictive control (MPC),[169] and fuzzy logic.[170] PID alters insulin delivery according to the difference from target glucose (proportional), the area under the curve between measured and target glucose (integral), and the rate of change of measured glucose (derivative).[171,172] MPC predicts glucose concentrations over a predetermined time horizon to inform insulin delivery.[173] The fuzzy logic controller modulates insulin delivery based on a set of rules that imitates the reasoning of diabetes practitioners, which in turn are based on common medical knowledge and the experience of traditional treatment.[172] Currently there is no "optimal" algorithm; comparisons among different control algorithms[174–176] have been hindered by heterogeneous experimental designs.[174]

Besides control mechanisms, AID systems have other differentiating features. Early, fully CL studies demonstrated significant postprandial glycemic excursions and led to the use of a "hybrid" approach, meaning the user needs to manually bolus for carbohydrate intake.[168] With hybrid closed loop (HCL) only basal insulin delivery is adjusted based on sensor glucose values. Building on this, advanced hybrid closed loop (AHCL) systems incorporate automated correction boluses as part of the algorithmically modulated insulin delivery. Therefore, the differentiation between manual, or user initiated, and automated insulin delivery may be more meaningful than the classic categorization of insulin delivery as being either basal or bolus.

System targets are set in one of two ways; a treat-to-target approach with a single target glucose [e.g., 5.8 mmol/L (105 mg/dl)] or treat-to-range approach [e.g., 6.2–8.9 mmol/L (112–160 mg/dl)].[172]

9.2 | Benefits of AID

AID performance has been explored in controlled highly supervised in-clinic or transitional environments like hotels and camps.[177,178] These trials clearly demonstrated increased TIR and a concomitant reduction in time below range and led to home setting assessments.

Some outpatient trials of these devices have been conducted using an RCT design,[179–187] while others have been single arm trials.[188–194] The RCTs have demonstrated the efficacy of both HCL and AHCL to achieve ~10%–15% increase TIR (3.9–10 mmol/L, 70–180 mg/dl) when compared to conventional pump therapy, SAP, PLGS, or HCL to ACHL.[179–187] Similar findings in change in TIR from baseline data collection periods have been noted in the single-arm trials.[188–194] (Table 3). These findings hold true regardless of the age of participants; importantly AID benefits have been demonstrated in very young children aged 2–5 years, children aged 6–13 years, adolescents, and young adults (Table 3). In addition to the increased TIR, longer outpatient studies have also demonstrated that AID use has led to a concomitant reduction in HbA1c by 0.3%–0.7%.[179,181–185,187–194]

A post-hoc analysis conducted on data from the Diabetes Control and Complications Trial (DCCT), demonstrated that a 10% lower TIR was strongly associated with risk of retinopathy progression and development of microalbuminuria (hazard rates of 64% and 40%, respectively).[30] Importantly, this data was derived from 7-point fingerstick testing conducted during daytime hours in the DCCT, and so it may underestimate the true TIR. Yet, it would imply that the observation of ~10% increase in TIR in recent clinical trials of AID systems will decrease rates of microvascular complications in youth using these systems.

9.3 | Initiating AID and persisting with system use

Historically, determining ideal candidates for initiating diabetes technology use has often been based on how engaged a person with diabetes, or for children their caregivers, are with diabetes management. Engagement could be demonstrated by performing a minimum number of glucose checks per day, attending a certain threshold of medical visits per year, or achieving a target HbA1c level as a crude proxy estimate for treatment adherence.[195] Yet, these criteria are not evidence-based, may introduce substantial bias into determining who would be suitable candidates, and deny access to technology for children who could benefit greatly. This bias could contribute to disparities noted in device access. Data from the Control IQ pivotal trial demonstrated

TABLE 3 Automated Insulin Delivery (AID) studies that have enrolled very young children, children, and adolescents

AID system	Study duration and design	Comparison group/ baseline data collection on	Population	Baseline	Glycemic outcomes assessed	Difference [between groups or from baseline]
Very young children						
Medtronic 670 G[188]	3-month, single arm-study	Baseline pump or SAP	$N = 46$ Age = 4.6 ± 1.4 years	HbA1c 8.0 ± 0.9% TIR 55.7 ± 13.4	HbA1c 7.5 ± 0.6% TIR 63.8 ± 9.4%	ΔHbA1c −0.5% ΔTIR +8.1%
CamAPS[179]	16-week per treatment, two period, randomized crossover trial	HCL SAP	$N = 74$ [$N = 39$ HCL and $N = 35$ SAP first group] Age 5.6 ± 1.6 years	HbA1c 7.3 ± 0.7% TIR 61.2 ± 10.1%	HbA1c 6.6 ± 0.6% TIR 71.6 ± 5.9% HbA1c 7.0 ± 0.7% TIR 62.9 ± 9.0%	ΔHbA1c −0.4% ΔTIR +8.7% [paired differences]
Medtronic 670G[187]	8-week per treatment, randomized, controlled, crossover trial	HCL SAP	$N = 18$ Age 5.4 ± 1.1 years	HbA1c 7.0 ± 0.7% TIR 65.9 ± 12.6%	HbA1c 6.7 ± 0.3% TIR 72.7 ± 6.1% HbA1c 6.8 ± 0.3% TIR 67.5 ± 9.6%	ΔHbA1c −0.3% from baseline ΔTIR +6.8% from baseline
Omnipod 5[194]	3-month single arm-study	Baseline MDI, pump, SAP, HCL	$N = 80$ Age 4.7 ± 1.0 years	HbA1c 7.4 ± 1.0% TIR 57.2 ± 15.3%	HbA1c 6.9 ± 0.7% TIR68.1 ± 9.0%	ΔHbA1c −0.55 ΔTIR +10.9%
Children (6–13 years)[a]						
Medtronic 670 G[193]	3-month single arm-study	Baseline pump or SAP	$N = 105$ Age 10.8 ± 1.8 years	HbA1c 7.9 ± 0.8% TIR 56.2 ± 11.4%	HbA1c 7.5 ± 0.6% TIR 65.0 ± 7.7%	ΔHbA1c −0.4% ΔTIR +8.8%
Medtronic 670G[187]	8-week per treatment, randomized, controlled, crossover trial	HCL SAP	$N = 20$ Age 11.6 ± 1.7 years	HbA1c 7.7 ± 0.9% TIR 55.1 ± 11.6%	HbA1c 7.1 ± 0.5% TIR 69.1 ± 7.8% HbA1c 7.5 ± 0.7% TIR 53.9 ± 14.1%	ΔHbA1c −0.6% from baseline ΔTIR +14%
Omnipod 5[189]	3-month single arm-study	MDI, pump, SAP, HCL	$N = 112$ Age 10.3 ± 2.2 years	HbA1c 7.67 ± 0.95% TIR 52.5 ± 15.6%	HbA1c 6.99 ± 0.63 TIR 68.0 ± 8.1%	ΔHbA1c −0.71% ΔTIR +15.6%
Diabeloop Generation 1 (DBLG1)[186]	6-week cross-over study [outpatient phase]	HCL SAP	$N = 17$ Age 8.2 ± 1.6 years	HbA1c 7.2 ± 0.5% TIR n/a	HbA1c n/a TIR 66.2 ± 1.5% HbA1c n/a TIR 58.7 ± 1.5%	ΔHbA1c n/a ΔTIR +7.5%
Tandem Control IQ[183]	16-week RCT, parallel group	AHCL SAP	$N = 78$ Age 11.3 ± 2.0 years $N = 23$ Age 10.8 ± 2.4 years	HbA1c 7.6 ± 1.0% TIR 53 ± 17% HbA1c 7.9 ± 0.9% TIR 51 ± 16%	HbA1c 7.0 ± 0.8% TIR 67 ± 10% HbA1c 7.6 ± 0.9% TIR 55 ± 13%	ΔHbA1c −0.4% ΔTIR +11%
Adolescents and adults (>14 years)						
Medtronic 670G[191,192]	3-month single arm-study	Pump or SAP	$N = 124$ Age 21.7 years *Adolescent cohort* $N = 30$ Age 16.5 ± 0.9 years	HbA1c 7.4 ± 0.9% TIR66.7% ± 12.2% *Adolescent cohort* HbA1c 7.7 ± 0.84% TIR60.4% ± 10.9%	HbA1c 6.9 ± 0.6% TIR 72.2% ± 8.8% *Adolescent cohort* HbA1c 7.1 ± 0.6% TIR67.2% ± 8.2%	ΔHbA1c −0.5% ΔTIR +5.5% From baseline *Adolescent cohort* ΔHbA1c −0.6% ΔTIR +6.8% From baseline

TABLE 3 (Continued)

AID system	Study duration and design	Comparison group/ baseline data collection on	Population	Baseline	Glycemic outcomes assessed	Difference [between groups or from baseline]
Medtronic 670G vs AHCL[184]	12-week per treatment, two period, randomized crossover trial	AHCL	*N* = 113 Age 19 ± 4 years	HbA1c 7.9 ± 0.7% TIR 57% ± 12%	HbA1c 7.4 ± 0.8% TIR 67% ± 8%	ΔHbA1c −0.5% ΔTIR +10% From baseline
		HCL (Medtronic 670G)			HbA1c 7.6 ± 0.6% TIR 63% ± 8%	ΔHbA1c −0.3% ΔTIR +6% From baseline
Medtronic 780G[190a]	4-week per treatment, two period, randomized crossover trial	AHCL	*N* = 60 Age 23.5 years	HbA1c 7.6 TIR 59.0 ± 10.4	HbA1c n/a TIR70.4 ± 8.1%	ΔHbA1c n/a ΔTIR +14.4% [paired difference]
		PLGS			HbA1c n/a TIR 57.0 ± 11.7%	
Medtronic 780G A-HCL[190]	3-month single arm-study	Baseline with pump, SAP, or HCL	*N* = 157 Age 38.3 ± 17.6 years *Adolescent cohort* *N* = 39 Age 16.2 ± 2.1 years	HbA1c 7.5 ± 0.8% TIR 68.8 ± 10.5% *Adolescent cohort* HbA1c 7.6 ± 0.8% TIR 62.4 ± 9.9%	HbA1c 7.0 ± 0.5% TIR 74.5 ± 6.9% *Adolescent cohort* HbA1c 7.1 ± 0.6% TIR 72.7 ± 5.6%	ΔHbA1c −0.5% ΔTIR +5.7% *Adolescent cohort* ΔHbA1c −0.5% ΔTIR +10.4%
Cambridge MPC (Medtronic 640G pump and Enlite 3 sensor)[181]	3-month, two-arm randomized controlled trial	HCL	*N* = 46 Age: 22 (range 13–36) years	HbA1c 8.0 ± 0.6% TIR 52 ± 10%	HbA1c 7.4 ± 0.6% TIR 65 ± 8%	ΔHbA1c −0.36% ΔTIR +10.8%
		SAP	*N* = 40 (control) Age: 21 (range 11–36) years	HbA1c 7.8 ± 0.6% TIR 52 ± 9%	HbA1c 7.7 ± 0.5% TIR 54 ± 9%	
Tandem Control IQ[182]	6-month randomized controlled trial	AHCL	*N* = 112 Age 33 ± 16 years	HbA1c 7.4 ± 0.96% TIR 61 ± 17%	HbA1c 7.06 ± 0.79% TIR 71 ± 12%	ΔHbA1c −0.33% ΔTIR +11%
		SAP	*N* = 56 Age 33 ± 17 years	HbA1c 7.4 ± 0.76% TIR 59 ± 14%	HbA1c 7.39 ± 0.92% TIR 59 ± 14%	
Omnipod 5[189]	3-month single-arm study	MDI, pump, SAP or HCL	*N* = 128 Age 36.9 ± 13.9 years	HbA1c 7.16 ± 0.86% TIR 64.7 ± 16.6%	HbA1c 6.78 ± 0.68% TIR 73.9 ± 11.0%	ΔHbA1c −0.38% ΔTIR + 9.3%
Diabeloop Generation 1 (DBLG1)[185]	12-week per treatment, two period randomized crossover trial	HCL	*N* = 63 Age 48.2 ± 13.4 years	HbA1c 7.6 ± 0.9% TIR n/a	ΔHbA1c from baseline −0.29% TIR 68.5 ± 9·4%	ΔHbA1c −0.15% ΔTIR +9.2% [paired difference]
		SAP			ΔHbA1c from baseline −0.14% TIR 59.4 ± 10.2%	

Note: ΔHbA1c and ΔTIR indicates the difference from baseline or between groups of HbA1c and time in range 3.9–10 mmol/L (70–180 mg/dl), respectively.

Abbreviations: A-HCL, advanced hybrid closed loop; AID, automated insulin delivery; HbA1c, hemoglobin A1c; HCL, hybrid closed loop; MDI, multiple daily injections; SAP, sensor augmented pump; PLGS, predictive low glucose suspend; TIR, time in range 3.9–10 mmol/L (70–180 mg/dl).

[a]For studies including those age 6–13 years but limited data by age group they are included in the table under adolescent/adult data.

that, while all participants in the 14–71 year old cohort had improved TIR, those with baseline HbA1c ≥8.5% had the greatest reduction in time above range, while those with HbA1c <6.5% primarily benefited from reductions in time below range.[196] Recently, real-world Control IQ system data from those age ≥6 years have demonstrated that those with a higher initial glucose management index (GMI), which estimates average HbA1c concentration based on mean sensor glucose values, showed substantial improvement over time.[197] Real-world use analyses of 670G use in 14,899 users (no age demographics provided), demonstrated that for those with a GMI <7%, TIR improved slightly from 76.1% to 78.7%, while for the group whose GMI was >8%, improvement was more substantial from 34.7% to 58.1%.[198] These data provide compelling evidence that all with diabetes can benefit from advanced diabetes technologies and providers should not limit access to this therapy. Additionally, they should seek to advocate for their safe incorporation into the management plan and provide education and support to help children and families use the devices consistently and as intended.

Once technology use has begun, persistent use is essential for success. Users have reported that system-mandated exits (user has to revert to using conventional pump settings because automation is unavailable) can lead to user frustration and ultimately discontinuation of device use.[199,200] A real-world prospective trial with the first HCL system with 80 participants, of whom 30% were <18 years old, noted more than half of the participants, despite endorsing adequate training on the system, experienced sleep interruption due to alarms and 40% did not like the frequency of system-initiated reversion to open loop insulin.[201] Next generation systems have benefited from continued evolution, incorporate factory calibrated sensors and have eliminated numerous mandated exits. The need to revert to open loop is primarily dictated by times when sensor data are not available. Real-world assessment of device use has shown increased wear times with both the Tandem t:slim X2 with Control-IQ™ (Tandem, San Diego, CA) and the MiniMed™ 780G system (Medtronic, Northridge, CA).[202–204] Yet, it is imperative that people with diabetes, and their families, have realistic expectations of what devices can and cannot do and receive training on system use. This is reviewed further below in the behavioral section.

9.4 | Questioning the need for alternative approaches: Diluted insulin and do-it-yourself (DIY) systems

9.4.1 | Diluted insulin

Prior to recent trials, consideration had been given to the use of diluted rapid-acting insulin analogs in AID for very young children to reduce mechanical delivery errors and enable more consistent absorption due to the larger volume of the subcutaneous insulin depot. Although early studies performed in controlled settings[125–127] showed reduced glycemic variability and lower risk of time below range with diluted insulin[125] a subsequent 3-week outpatient RCT conducted in children aged 1–7 years, did not demonstrate any benefit of diluted insulin when compared to a standard U100 rapid-acting analog.[205] Importantly, this study also highlighted that, compared to other age cohorts, very young children have higher day-to-day variability in insulin requirements.[206] This supports the recommendation for rapid adoption of AID in this population as other insulin delivery modes cannot respond to the constant changes in insulin needs.[206]

9.4.2 | Open-source systems

Recognizing the inherent delays in conducting clinical trials and obtaining regulatory approval for new technologies, the past decade has seen the creation of open-source automated insulin delivery systems. Through an online community, the DIY approach has been adopted by several thousand people with diabetes and their families. In silico studies have demonstrated the relative safety of the system through simulations with both meal bolus over- and underestimation as well as what might occur with delayed bolusing.[207] Additionally, a real-world prospective observational study in 558 users, with more than half being <25 years old, showed improvement in TIR and reductions in the incidence of severe hypoglycemic events with system use, suggesting these systems can be used safely and effectively.[208] As these systems do not have regulatory approval, health care professionals should be cautious about recommending these devices in preference to commercially available systems. Yet, when people with diabetes choose to use an open-source system, a consensus statement suggests that providers should support them.[209] Recently, an RCT in those aged 7–70 years comparing use of an open-source AID to a control group using CGM showed an increase in TIR of 10% in the AID group leading to an adjusted difference between groups of 14%.[210]

9.5 | Additional strategies to improve automated insulin delivery

People using AID often experience postprandial hyperglycemia. Several mitigation strategies have been tried. Ultra fast-acting insulin analogs have not demonstrated clinical benefits in short duration trials.[211–213] Intraperitoneal insulin delivery has also been proposed[214,215] with short duration studies showing increased TIR of 4.4–7.8 mmol/L (80–140 mg/dl).[216] Additionally, inhaled insulin has been tested in conjunction with AID during meals and led to reduced glycemic excursions and improved postprandial glucose levels; further exploration of this strategy may be warranted.[217] In addition to optimizing glycemia, this approach could reduce the peripheral hyperinsulinemia of subcutaneous insulin delivery, which may also lower risk of macrovascular complications.[218–220] For both intraperitoneal and inhaled insulin delivery, longer and larger scale studies are needed.

Adjunctive non-insulin therapies have also been tested with AID to mitigate post-meal glucose excursions. These proof-of-concept or short feasibility trials, lay the groundwork for potential use of agents like pramlintide, glucagon like peptide-1 (GLP-1) analogs, and sodium glucose cotransporter inhibitors.[221–223] Finally, the use of a bihormonal AID system that integrates both insulin and glucagon infusions has

TABLE 4 Modified CARES approach to understand and optimize AID use[236]

	Questions	Potential Implications
Calculate	*How does the system CALCULATE insulin delivery?* Identify the key features of insulin delivery algorithm (e.g., treat to target vs. treat to range)	
	Which components of insulin delivery are automated?	• Basal rate modulation • Automated Correction boluses • Meal identification
Adjust	*How can the user ADJUST insulin delivery?*	
	Which parameters can be ADJUSTED to individualize insulin delivery during automation (e.g., setting optimization for each system and age group)?	• Insulin to Carbohydrate Ratios • Correction factors/Sensitivity Factors • System targets/setpoints • Duration of insulin action • Basal rates
	Which parameters are fixed?	Review settings that do not impact or cannot be altered during automation
Revert	*When does (should) the system REVERT to open loop insulin delivery?*	
	When should the user choose to *REVERT* to open loop/no automations?	Identify times when the user should *choose to revert to* open loop (ketosis, steroid use)
	When will the system default to open-loop/no automation?	• Identify reasons for *system mandated exits* to open-loop • Seek to minimize frequency of these events
Educate	*What are important factors in regard to EDUCATION about the system and setting appropriate EXPECTATIONS?*	
	What are the key *EDUCATION* points for the advanced diabetes device?	Essential training (tips and tricks, best practices, necessary skills)
	What are the user expectations?	• Discuss frequency of sensor wear and time anticipated in automation • Create individualized goals for HbA1c targets and TIR • Identify system limitations (e.g., postprandial glycemia)
	Where can users and clinicians find additional *EDUCATION*?	Identify verified source of education, which may include those developed by • Manufacturers • Professional societies • Academic groups • Diabetes Advocacy Groups/Online communities
Sensor/ Share	*What SENSORS pair with the system? What are the SHARE capabilities?*	
	What are the relevant *SENSOR* characteristics for each paired sensor?	Identify the need for calibration and therapeutic blood glucose requirements, duration of sensor wear, transmitter characteristics
	What are the system capabilities for remote monitoring and cloud-based data sharing?	• Review options for data sharing • Strategize the use of sharing options according to individual needs • Identify privacy options (if any)

been an area of intense interest with promising findings from initial trials.[224–228] With the advent of stable liquid glucagon, testing of systems for commercial approval is now underway.[229]

Adapting for physical activity also remains problematic. Studies have explored bi-hormonal systems, reduction of pre-meal boluses prior to exercise, administration of a snack just prior to exercise, and integration of alternate signals like heart rate monitors to detect exercise.[230–234]

9.6 | Practical considerations for AID

To ensure success with adoption of AID technology, it will be important for clinicians to have a framework to integrate its use. The "CARES" strategy has been suggested to help clinicians conceptualize the differences between AID systems.[235,236] CARES can assist clinicians by posing five fundamental questions related to the person with diabetes and the proposed device (Table 4).

Tools to assist people with diabetes compare devices with their clinicians will be of great benefit. Some resources include the American Diabetes Association consumer guide (https://consumerguide.diabetes.org), Diabetes Wise (https://diabeteswise.org/), and the Panther Program (https://www.pantherprogram.org).

Systematic training of people transitioning to hybrid closed loop and advanced closed loop therapy is essential.[237–239] People with diabetes should be guided on methods to manage exercise. See ISPAD 2022 Consensus Guidelines Chapter 14 on Exercise in children and

adolescents with diabetes. Carbohydrate intake required for treatment of mild hypoglycemia often only requires 5–10 g with AID systems and may need to be reduced in the context of prolonged basal insulin suspension with other devices.

10 | BEHAVIORAL, PSYCHOSOCIAL, AND EDUCATIONAL CONSIDERATIONS OF INSULIN DELIVERY DEVICES

Uptake and sustained use of insulin delivery devices are associated with behavioral and psychosocial factors, including self-management demands, emotional considerations, family experiences, and social variables. Such factors may promote (e.g., supportive family involvement) or be barriers (e.g., diabetes distress) to optimal engagement in self-management behaviors. ISPAD 2022 Consensus Guidelines Chapter 15 on Psychological Care of children and adolescents with type 1 diabetes and the American Diabetes Association[32] highlight the importance of attending to the psychosocial needs of youth with diabetes and their families, which has implications for optimal use of diabetes technologies including insulin delivery devices.

Youth with T1D who use insulin pumps tend to experience benefits in health-related quality of life compared to MDI.[240–242] Parents may also experience improved quality of life.[243] Specific perceived benefits of pump therapy include increased autonomy in diabetes management, decreased diabetes burdens, and greater flexibility in eating.[241,244,245] However, psychosocial factors, such as depressive symptoms, may increase the risk for discontinuation of pump use.[98]

Fear of hypoglycemia is a common concern for people with diabetes and their caregivers.[11] LGS systems may reduce this fear, although data are limited. The CGM **T**iming of **I**nitiation of continuous glucose **M**onitoring in **E**stablished pediatric diabetes (TIME) trial was a multicenter RCT whose primary aim was to assess the impact of CGM initiation in comparison to starting pump therapy.[246] An exploratory sub study assessed fear of hypoglycemia using the Hypoglycemia Fear Survey.[247] Parents and children >10 years old had significantly reduced fear of hypoglycemia after 1 year of follow up; yet this was not related to CGM adherence nor were data obtained about whether participants were using the LGS feature.[247]

Early research found youth who were potential AID system users felt trusting the system was critical for uptake; children and adolescents emphasized concerns related to use at school and with peers, while parents' concerns prioritized accuracy and ensuring that systems stabilize glucose levels and reduce risk for long-term complications.[248] Studies of HCL systems in clinical and real-world settings suggest benefits for quality of life and well-being, including lower diabetes burden/distress (especially around meals), reduced fear of hypoglycemia and worries about glycemic excursions, less time spent thinking about diabetes, and improved treatment satisfaction.[241,249–253] There are also indications of perceived improvements in sleep for both youth and parents.[253,254]

However, AID device discontinuation has been estimated to occur in up to 30% of youth.[199,200] Psychosocial and behavioral barriers to use have been identified, including devices not being as "hands-off" as anticipated, perceived high workload required to maintain AID function, concerns about accuracy and distrust of the devices, dissatisfaction with the size/appearance of wearing multiple devices, physical discomfort, limitations to their use during physical activity or while bathing, limitations in remote monitoring access for parents, frustrations with technical glitches, and difficulties with required calibration of some devices.[251,255,256] AID devices that use factory calibrated CGM, which eliminate/minimize the need for BG checks with a glucometer, may reduce the burden associated with AID devices and improve sustainability of use, especially in youth.[257]

Evidence from qualitative research and self-report surveys suggests that caregivers are motivated for their children to use AID systems primarily to improve glycemic outcomes, reduce diabetes care burdens, and improve sleep.[209,258] As such, caregivers and youth may have high expectations of AID systems to drastically reduce or eliminate the need for diabetes self-management behaviors. To date, this is an unrealistic expectation, as all available AID systems require users to announce carbohydrate intake, deliver meal boluses and respond to system alerts. Evidence suggests that those youth with higher HbA1c and greater negative affect around diabetes self-management may have more positive expectations for AID device use.[259] Additionally, less knowledge about AID devices may result in overly optimistic expectations and greater risk of dissatisfaction with the device.[251] Thus, it is critical that diabetes care teams assess expectations, educate youth and caregivers about realistic expectations for these systems, and provide referrals for any psychosocial need that may be a barrier to optimal device use.

Education and device training are important to ensure effective use of insulin pump devices and to promote sustained device use and ongoing success.[238,239,260,261] For AID devices, a structured training program with frequent follow-up for new users is recommended to optimize device use. The training program should emphasize education on the basics of CGM use, required diabetes self-management tasks to optimize the device (i.e., pre-meal bolusing), and common troubleshooting for the specific device. It is imperative that users understand the safety principles of managing persistent hyperglycemia and infusion site failure (i.e., when to check ketones, change infusion site, and/or give insulin by injection). These principles are vital for safe use of any insulin pump therapy to prevent DKA and are equally applicable with use of advanced insulin delivery technologies. Users who discontinue HCL/AID devices are most likely to discontinue within the first 1–3 months of use.[199,200] Therefore, follow-up within the first month of use is helpful to assess system use and glucose trends, to allow the provider or diabetes educator an opportunity to identify early any challenges the user may be experiencing, and to provide an opportunity for targeted re-education to help the user overcome challenges and improve outcomes. Further, youth may benefit from adjustments to any modifiable pump settings (i.e., insulin to carbohydrate ratios) to improve glycemic outcomes when transitioning from MDI or a conventional insulin pump to AID, and a follow-up call in the first month provides the opportunity for the clinician to make these changes.

In sum, the current evidence base points to psychosocial and quality of life benefits from using insulin pumps, including conventional insulin pumps, SAP, LGS, PLGS, and AID systems. As insulin pump technologies continue to advance and offer opportunities for improved glycemic outcomes, interventions to reduce barriers to technology use are actively being investigated.[34] However, more clinically translatable research targeted to the needs and experiences of pediatric populations is needed on the best ways to break down barriers to uptake of insulin delivery devices and technologies and to prevent discontinuation.

10.1 | Practical considerations for behavioral, psychosocial, and educational considerations of insulin delivery devices

When integrating diabetes technology into the care of youth with diabetes, families of all backgrounds should be informed about the spectrum of insulin delivery devices from conventional pumps to AID systems. Clinicians should portray the use of insulin delivery devices and technologies as an option that can be a good fit for many youth and families, provide education and encourage youth and families to review vetted websites and device informational materials. Further, it is critical for the diabetes team to recommend the most advanced device technology that the person with diabetes is interested in and to not make assumptions about interest or capability. Clinicians should refrain from having youth and families "earn" the right to use devices (i.e., achieve a certain HbA1c before considering starting a device). If payers/insurance companies require logging or other documentation prior to device approval, convey that directly to the family and advise this is not a requirement of the diabetes care practice.

Assessing barriers to device uptake and use should be part of routine clinical practice. Providers should seek to work with the youth and their family on ways to break down barriers and increase facilitators of device use. This may require referral to a psychological care provider, who can teach problem-solving skills and other behavioral strategies to support device uptake and sustained use.[262]

10.1.1 | Setting realistic expectations

With integration of any diabetes technology, it is critical for people with diabetes and their families to understand what devices can and cannot do. Ensuring realistic expectations for glycemic outcomes and the effort required for successful use of technologies is essential. This may be especially important in those who have suboptimal glycemia, those who have had challenges with engagement with the current treatment plan, and/or those with higher burnout/mood concerns in the past.

When transitioning to an AID system, people with diabetes and their caregivers should be advised that although glycemia will improve they should expect to experience some variability. As evidenced in the clinical trials, improvements in nocturnal glycemia are anticipated to be the greatest. Youth with diabetes and their families must understand that glucose fluctuations will still occur, especially after meals and that people with diabetes will need to receive meal boluses to attain glycemic targets. Finally, with the transition to new devices, users should be prepared to allow at least a 1 month adjustment period. In addition to the person with diabetes and their caregiver(s) acclimating to using the new insulin delivery system, changes in the total daily insulin dose may influence how the algorithm functions; that is, the parameters for insulin delivery are linked to the total daily dose for some systems, and alterations in insulin requirements will seamlessly impact automation for systems with adaptivity. Further, adjustments to modifiable pump settings, especially insulin to carbohydrate ratios, are generally needed to optimize glycemic outcomes.

10.1.2 | Critical components of training

Standardized training is critical. Three overarching themes should be reviewed: 1. basics of device use, 2. CGM education, 3. hyperglycemia and other troubleshooting strategies. With each insulin delivery device, people with diabetes and their families should be trained on the basics of device use as well as unique features of the device (i.e., sleep or exercise features for AID systems or temporary basal rates for pumps and SAP). With any system that can alter insulin delivery based on sensor glucose values, CGM education will be a cornerstone of care. For success, with SAP, LGS, PLGs, and AID systems consistent CGM use is required. Discussing any identified challenges to CGM wear (i.e., alarm fatigue, skin irritation, inconsistent wear) and problem-solving solutions will be crucial to minimize the risk of device discontinuation. As with all subcutaneously infused insulin, there is a risk of infusion set failure, which may lead to persistent hyperglycemia and DKA. To minimize this risk, users should be advised to check for ketones if they have persistent hyperglycemia, change their infusion set, and give an insulin injection with a pen or syringe. See ISPAD 2022 Consensus Guidelines Chapter 12 on Sick day management in children and adolescents with diabetes. Clinicians should review the most common issues youth and families are likely to face and provide a framework for troubleshooting. Additionally, users should be able to call device manufacturers for additional technical assistance. This requires manufacturers to employ trained personnel to answer such calls and work with users who may have varying degrees of numeracy and literacy skills.

Clinicians should encourage families to use the AID as intended to obtain optimal outcomes. Users should be advised to avoid "tricking" the system and encouraged to "work with it, not against it". For example, youth with diabetes and their families should only announce food intake by entering carbohydrate amounts if the person with diabetes will really eat them and follow the bolus calculator recommendations. Increases in insulin delivery by AID algorithms are incorporated into insulin on board calculations and subtracted from bolus dose calculations. Overriding the bolus calculator to give more insulin than is recommended may result in

hypoglycemia because the user may be unaware that there may be a lot of insulin on board from automated insulin delivery. Families should be counseled to trust the system; ensuring they are equipped with skills to manage unanticipated hyper- or hypoglycemia will help them feel comfortable as they develop this trust. Finally, families should be encouraged to talk to their diabetes team if they have concerns about how the algorithm is working or observe high or low blood glucose patterns that may signal needed adjustments to modifiable parameters in the pump (i.e., insulin to carbohydrate ratios, correction factor) or behavioral modifications (e.g., bolus prior to eating) to improve glycemic outcomes.

If psychosocial needs are reported or identified, refer to psychological care provider.[263] For further information, see the ISPAD 2022 Consensus Guidelines Chapter 15 on Psychological Care of children and adolescents with type 1 diabetes.

11 | CONCLUSION

Just as our everyday lives have vastly changed with integration of new technologies including computers, smartphones, and the increased connectivity of devices, the technological revolution has had an enormous effect on the management of diabetes and especially modes of insulin delivery. It is reasonable to expect that in the years ahead there will be significant growth in this aspect of diabetes care and that these mechanical solutions will afford people with diabetes, and their families, improved ability to attain glycemic targets while reducing the burden of diabetes care. With integration of more physiologic insulin delivery afforded by AID systems, it is possible that the range of glucose levels that currently define target range, specifically 3.9–10 mmol/L (70–180 mg/dl) may be further tightened [e.g., 3.9–7.8 mmol/L (70–140 mg/dl)]. Data from people without diabetes highlight the exquisite regulation afforded by endogenous insulin production, with mean glucose being 5.4–5.5 mmol/L (98–99 mg/dl) and 96% of time spent in this tighter target range.[264] The true test of new technologies will be to see how they can reduce glycemic variability while achieving greater TIR and improve quality of life. Clinicians must seek methods to remain abreast of new technology developments to optimize uptake and use. Integration of technology into clinical care will also require understanding of the cost–benefit of therapies to justify payer coverage. Indeed, as many of these technologies are expensive, further understanding of the health economics and relevant policies/regulations will provide valuable information for people with diabetes, clinicians, as well as payers.

This chapter has reviewed evidence on insulin delivery devices in children, adolescents, and young adults with the aim of providing practical advice and approaches to their use. Updates are anticipated in this rapidly evolving area of research and practice.

CONFLICT OF INTEREST

J.L.S. reports having received speaker honoraria from Eli Lilly, Insulet, Medtronic, and Zealand and serves on advisory boards of Bigfoot Biomedical, Cecelia Health, Insulet Corporation, Medtronic Diabetes, JDRF T1D Fund, and Vertex. She has been a consultant for Insulet and Medtronic. J.L.S.'s institution received research grant support from JDRF, Medtronic, Insulet, and NIDDK. M.S. reports research grant support, paid to her institution, from Tandem Diabetes Care, Insulet, Medtronic, JDRF, and NIDDK. T.S. has no conflict to disclose. L.R. reports speaker fees from Sanofi, Pfizer, NovoNordisk. T.B. reports speaker fees, consulting honoraria or research support from AstraZeneca, Ascensia, DexCom, Medtronic, NovoNordisk, Roche, Sanofi, and Ypsomed. Since 2021, he is member of the Expert group for medical devices of the European Medicines Agency. A.G. received speaker honoraria from Ypsomed. A.G.'s institution received research support from the European Commission (H2020 program). J.V. has no conflict to disclose. M.E.H. receives research grant support from NIDDK, JDRF, and The Leona M. and Harry B. Helmsley Charitable Trust. C.B. has been a consultant for Insulet. L. A.D. reports that in the last 3 years she has consulted for Vertex and served on a Mannkind, Merck, and Abata adivosry board. She has also recieved research support to her instiution from Caladrius, Lilly, Mannkind, Medtronic, Provention, and Zealand.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13421.

AUTHOR CONTRIBUTIONS

JLS reviewed the literature, drafted sections of the guidelines, oversaw completion of the first draft of the guidelines, and edited the manuscript. MS, TD, LR, TB, AG, JV, MEH and CB reviewed the literature, provided drafts of sections and edited the manuscript. LAD outlined the guidelines, reviewed the literature, edited the manuscript, and served as the senior author. The authors gratefully acknowledge the editorial assistance of Dr. Leena Priyambada.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Sherr JL, Schoelwer M, Dos Santos TJ, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Insulin delivery. *Pediatr Diabetes*. 2022;23(8):1406-1431. doi:10.1111/pedi.13421

Received: 24 October 2022 | Accepted: 27 October 2022

DOI: 10.1111/pedi.13444

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Microvascular and macrovascular complications in children and adolescents with diabetes

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1 | WHAT IS NEW OR DIFFERENT

1. Addition of screening and treatment recommendations for vascular complications in type 2 diabetes (T2D)
2. Update of urinary albumin/creatinine ratio (ACR) thresholds for the diagnosis of increased albuminuria
3. Recommendation for eGFR monitoring in young people with diabetes
4. Change in frequency of retinopathy screening for type 1 diabetes (T1D)

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

Screening for and prevention of complications (Table 1).

2.1 | Prevention

- Children and adolescents with diabetes should receive intensive education and treatment to prevent or delay the onset and progression of vascular complications. **A**
- Achievement of glycemic targets will reduce the risk for onset and progression of diabetes vascular complications. **A**
- Screening for vascular complications should be performed preconception and in each trimester of pregnancy. **B**

2.2 | Albuminuria

- Screening for increased albuminuria in T1D should start at puberty or from age 11 years, whichever is earlier, with 2–5 years diabetes duration, and repeated annually thereafter. **B**

- Screening for increased albuminuria in T2D should start at diabetes diagnosis and repeated annually thereafter. **B**
- Consider confirming persistently increased albuminuria by first morning urine sample for urinary albumin/creatinine ratio (ACR) to rule out orthostatic proteinuria. **E**
- Because of biological variability, it is recommended to use 2 of 3 urine samples over a 3–6-month period as evidence of increased albuminuria. Confounders are exercise, menstrual bleeding, urinary tract infections, fever, non-diabetic kidney diseases and marked hyperglycemia. It is advised to repeat abnormal screening tests because elevated albuminuria may be transient. **E**
- Consider screening of eGFR in T1D at puberty or from age 11 years, whichever is earlier, with 2–5 years diabetes duration. **E**
- Consider screening of eGFR starting at diabetes diagnosis in youth with T2D. **E**
- Consider work-up for non-diabetic kidney disease in all children and adolescents with T2D and T1D with Chronic Kidney Disease (CKD) stage A3 (UACR >300 mg/g or 30 mg/mmol) or G2-5 (eGFR <90 ml/min/1.73m^2) including urinalysis, renal ultrasound and immune work-up. **E**
- Optimize glycemia to prevent the onset and progression of albuminuria. **B**
- Optimize blood pressure (BP) to prevent the onset and progression of albuminuria. **B**
- Consider angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in adolescents with persistently elevated albuminuria to prevent progression to proteinuria. **E**
- Monitoring for changes in BP, serum creatinine and potassium within 2 weeks of initiation of an ACE inhibitor or ARB, and annually thereafter. **E**
- Consider holding ACE inhibitors or ARB during episodes of dehydration and DKA. **E**
- Contraception counseling is required in post-pubertal females with diabetes that are treated with an ACE inhibitors or ARB due to potential teratogenicity. **E**

2.3 | Retinopathy

- Screening for diabetic retinopathy (DR) should start at puberty or from age 11 years with 2–5 years diabetes duration. **B**
- Screening for DR in T2D should start at diabetes diagnosis. **C**
- Screening for DR should be performed by an ophthalmologist, optometrist, or a trained experienced observer through dilated pupils via bio-microscopy examination or fundal photography. **B**
- For those with diabetes duration less than 10 years, mild non-proliferative DR (NPDR, i.e., microaneurysms only) and optimal glycemic targets, biennial screening assessment is recommended. The frequency of retinopathy screening can be reduced to 3 years if there is no retinopathy at first assessment but needs to be more frequent if there are high-risk features for visual loss. **E**
- Because of potential worsening of DR in people with diabetes with long-standing suboptimal glycemia that subsequently rapidly improves, ophthalmological monitoring is recommended before initiation of intensive treatment and at 3-monthly intervals for 6–12 months thereafter, particularly if moderate NPDR or worse at the time of intensification. **E**
- Prompt referral of young people with diabetes with vision threatening retinopathy (severe NPDR or worse and/or diabetic macular edema [DME]) to an ophthalmologist with experience in the management of DR is recommended. **A**
- Laser treatment and intravitreal injections of anti-VEGF agents reduce the rate of visual loss for individuals with vision-threatening stages of retinopathy (severe NPDR or worse and/or DME). **A**

TABLE 1 Screening recommendations for vascular complications

	When to commence screening?	Screening methods
Nephropathy	**T1D:** at puberty or age 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Urinary ACR Confirm with 1st morning urine sample Frequency: annually
Retinopathy	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Fundus photography or mydriatic ophthalmoscopy Frequency: every 2–3 years
Neuropathy	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	History Physical examination Clinical tests Frequency: annually
Macrovascular disease	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Lipid panel every 3 years BP at least annually; ideally at every clinic visit

2.4 | Other ocular conditions

- A comprehensive eye examination is also recommended to detect cataracts, major refractive errors, or other ocular disorders at the time of retinopathy screening or earlier if there are any visual disturbances. **E**

2.5 | Neuropathy

- Screening for peripheral neuropathy in young people with T1D should start at puberty or from age 11 years with 2–5 years diabetes duration and be repeated annually thereafter. **B**
- Screening for diabetic neuropathy in T2D should start at diabetes diagnosis and be repeated annually thereafter. **B**
- Screening for peripheral neuropathy includes assessment of temperature or pinprick sensation, vibration and ankle reflexes.

Screening for cardiac autonomic neuropathy includes assessment of orthostasis and heart rate variability (HRV). **E**

2.6 | Blood pressure

- Measure BP at least annually and preferably at every clinic visit from diagnosis of T1D or T2D. **E**
- For people with diabetes <13 years of age hypertension is defined as average systolic (SBP) and/or diastolic BP (DBP) ≥ 95th percentile for sex, age, and height on three or more occasions. For people with diabetes ≥13 years of age, hypertension is defined as average SBP and/or DBP ≥130/80 mm Hg. **B**
- Consider use of 24 h ambulatory BP measurements for screening and especially confirmation of hypertension. **E**
- Initial treatment of hypertension consists of weight loss, limitation of dietary salt, and increased physical activity. **E**
- If unable to achieve normal BP after 6 months of lifestyle interventions, an ACE inhibitor or other BP lowering agent is recommended. **E**
- ACE inhibitors have been effective and safe in children in short-term studies **A,** but are not safe during pregnancy, which needs to be discussed with young women of childbearing potential. **B**

2.7 | Lipids

- Screening for dyslipidemia is recommended soon after diagnosis (when glycemia is stabilized) in all young people with T1D from age 11 years. **E** If lipid levels are normal, repeat screening every 3 years. If there is a family history of hypercholesterolemia, early cardiovascular disease (CVD) or if the family history is unknown, start screening as early as age 2 years. **E**
- Screening for dyslipidemia in T2D should start at diabetes diagnosis (when glycemia is stabilized) and repeated annually. **C**
- Screening with a fasting lipid profile is ideal but often not practical in youth with diabetes. Non-fasting lipids screening may be obtained and if triglycerides or LDL levels are elevated, a fasting lipid profile would then be indicated. A fasting sample is required to monitor therapy. **E**
- High LDL cholesterol is defined as >2.6 mmol/L (100 mg/dL). **E** If this is present then interventions to improve glycemia, dietary changes and increased exercise should be instituted. Dietary interventions should restrict saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day and around 10% of calories from monounsaturated fats.
- If the above interventions do not lower LDL cholesterol <3.4 mmol/L (130 mg/dL), statins may be considered in children from age 10 years (Table 2). **E**
- Contraception counseling is required in post-pubertal females with diabetes who are treated with statins due to their potential teratogenicity. **E**

TABLE 2 Recommended threshold values for different parameters for intervention and primary prevention of microvascular and CVD in children and adolescents with T1D

Threshold value	Type of intervention
<13 years: BP >90th percentile for age, sex and height ≥13 years: BP >120/80 mm Hg	Lifestyle intervention: exercise, diet and less screen time
<13 years: BP >90th percentile despite lifestyle intervention ≥13 years: BP >120/80 mm Hg despite lifestyle intervention	ACE inhibitor or other BP lowering agent If elevated albuminuria is present: ACE inhibitor or ARB
<13 years: BP >95th percentile for age, sex and height ≥13 years: BP > 130/90 mm Hg	Lifestyle intervention and ACE inhibitor or other BP lowering agent If elevated albuminuria is present: ACE inhibitor or ARB
LDL-cholesterol >2.6 mmol/L (100 mg/dL)	Dietary and lifestyle intervention
LDL-cholesterol >3.4 mmol/L (130 mg/dL)	Statin

2.8 | Lifestyle

- Prevention or cessation of smoking will reduce progression of albuminuria and cardiovascular disease. **B**

2.9 | Macrovascular disease

- Screening of BP and lipids is recommended, as above. The benefit of routine screening for other markers of macrovascular complications outside the research setting is unclear. **E**

2.10 | Type 2 diabetes

- Screening for all complications should commence at diagnosis. Attention to risk factors should be escalated because of the increased risk of complications and mortality. **B** (See also the ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes).

3 | INTRODUCTION

The long-term vascular complications of diabetes include diabetic kidney disease (DKD), retinopathy, neuropathy, and macrovascular disease. The outcomes are:

- Kidney failure and hypertension due to DKD.

- Visual impairment and blindness due to DR.
- Pain, paresthesia, and loss of sensation due to peripheral neuropathy.
- Postural hypotension, gastroparesis, diarrhea, bladder paresis, and impotence, due to autonomic neuropathy.
- Cardiac disease, peripheral vascular disease, and stroke due to macrovascular disease.

These guidelines include evidence-based recommendations for prevention, screening, and treatment of these complications. Complementary information and guidance will also be provided in the ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes in the Youth and Chapter 25 on Managing Diabetes in Limited-Resource Setting.

Clinically evident diabetes-related vascular complications are rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of T1D, and already at onset in T2D. Please note that detailed management of advanced disease will not be covered in this chapter.

Childhood and adolescence are periods during which intensive education and treatment may prevent or delay the onset and progression of complications.[1] There has been a declining incidence of vascular complications in T1D reported in many areas with specialized clinics.[2,3] This has occurred over a period of time during which there have been major changes in and intensification of diabetes management, better identification of risk factors, and the advent of regular screening for complications. There is no evidence that this is a worldwide occurrence: in areas where health care is suboptimal, a greater risk of complications remains.[4] Overall, vascular complications continue to be a key contributor to premature mortality in young people with onset of diabetes during childhood.[5,6]

Although youth-onset T2D remains an uncommon disease in many countries, the incidence of this condition is projected to increase by 600% from 2017 to 2060.[7,8] Compounding this increase, youth-onset T2D exhibits a more extreme metabolic phenotype compared to adult-onset T2D, including greater insulin resistance and more rapid deterioration of pancreatic β-cell function.[9,10] These factors contribute to increased risk for vascular complications,[10–14] as highlighted in a recent systematic review,[15] and data from the 2021 Treatment Options for T2D in Adolescents and Youth (TODAY) 2 outcome study.[16] The burden of micro- and macrovascular complications is greater in youth-onset T2D compared to youth-onset T1D.[11]

3.1 | Interventional studies of intensive glycemic management

The diabetes control and complications trial (DCCT) was a multicenter, randomized controlled trial (RCT) involving 1441 people with diabetes with T1D conducted in North America from 1983 to 1993.[17] Study participants included 195 adolescents (aged 13–17 years), who were randomized to either intensive or conventional treatment. The DCCT provided unequivocal evidence that intensive diabetes treatment and improved glycemia conferred a significant risk reduction for microvascular complications compared with conventional treatment.[17] After completion of the DCCT (a median duration of participation of 6.5 years in the whole group), the epidemiology of diabetes interventions and complications (EDIC) study continued to follow the cohort. The EDIC study demonstrated that the positive effect of earlier intensive treatment continued after the end of the intervention: that is, that there was a "metabolic memory" effect of improved glycemia, now referred to as a "legacy effect."[18–20] During the EDIC study, a positive effect of the intensive therapy on macrovascular disease was also identified with a 50% reduction in cardiovascular events over 17 years[21,22] Benefits have persisted after 30 years of follow-up, resulting in substantial benefits in the incidence of retinopathy (5% vs. 45%), kidney failure (0% vs. 5%), clinical neuropathy (15% vs. 50%), myocardial infarction (3% vs.5%), stroke (3% vs. 5%) and death (6% vs. 20%). In addition, there was a gain of 1.62 quality of life years and reduced healthcare costs.[15,23]

Contemporary long-term follow-up studies continue to support the importance of achieving glycemic targets as the most important determinant of vascular complications in youth with T1D.[24] Similarly in the TODAY2 study, HbA1c was among the strongest risk factors for the onset of micro- and macrovascular complications over 15 years in youth with T2D.[16]

3.2 | Other risk factors for the development of complications

Longer duration of diabetes, older age and puberty are well-known risk factors for complications. In addition, a higher prevalence of microvascular complications has been reported for adolescent girls compared with boys.[25,26] The pre-pubertal years of diabetes duration have a significantly lesser impact on complication.[27] However the risk of vascular complications is greater for those living with diabetes during puberty, compared to young people who develop diabetes after puberty.[28] For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated albumin excretion rate.[29] Longitudinal studies have also reported that younger age of T1D onset, particularly before puberty, is associated with a longer time free of complications such as nephropathy and retinopathy,[27] but in the long-term this initial advantage disappears.[25] A recent study has developed a prediction model for kidney failure in adults with T1D, which includes age, sex, diabetes duration, estimated glomerular filtration rate (eGFR), albuminuria, systolic BP, HbA1c, smoking, and previous cardiovascular disease (CVD).[30] Incorporation of such models in clinical practice may have the potential to individualize care according to individual risk.

High rates of cardiovascular risk factors have been reported in children and adolescents with T1D.[5,31–33] The SEARCH study reported that 26% youth with T1D were overweight, 14% had obesity, 13% hypertension, and 29% dyslipidemia.[5] Of note, a clustering of these risk factors was associated with high rates of multiple vascular complications.[23] The prevalence of cardiometabolic risk factors increases with long T1D duration; however, they can be present even shortly after diagnosis.[33,34]

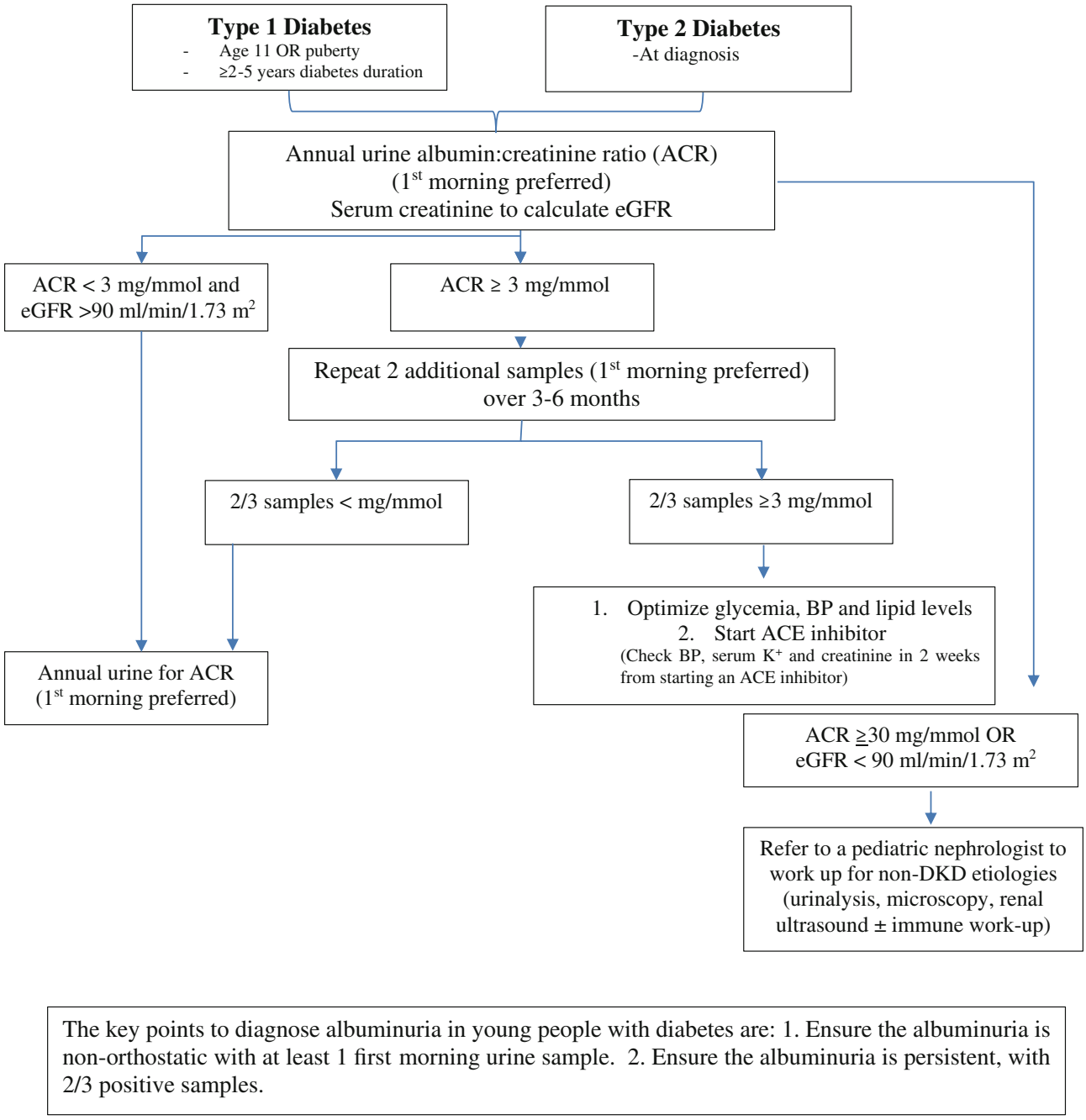

FIGURE 1 Diabetes kidney disease (DKD) screening algorithm in young persons with type 1 and 2 diabetes

Smoking is associated with an increased risk of developing persistent albuminuria.[35] The evidence for the effect of smoking on retinopathy is less clear. T1D and smoking interact to produce excess cardiovascular morbidity and mortality.[36]

High BP and alterations in the circadian BP rhythm have been associated with the risk of developing nephropathy, retinopathy and neuropathy in youth with T1D[37–39] Hypertension has a greater impact on CVD in individuals with than without diabetes,[40] and BP management is effective in decreasing cardiovascular morbidity and mortality in diabetes.[41]

Dyslipidemia was associated with DKD, retinopathy, neuropathy, and CVD in the DCCT/EDIC and other studies.[42–44] This included higher total LDL cholesterol and non-HDL cholesterol levels, as well as larger LDL particle size and higher apolipoprotein B.

Family history of CVD or the presence of risk factors for CVD increases the risk for DKD.[45–47] Higher BMI is a risk factor for nephropathy,[48,49] retinopathy,[50] neuropathy,[51] and CVD.[52] Indeed, a recent study found that higher BMI portends a more abnormal cardiovascular profile among adolescents with T1D, which is similar to, or less favorable than, youth with T2D on numerous metrics.[53]

Lifestyle issues also contribute to risk of complications; sedentary men with diabetes have higher mortality than active individuals.[54] Celiac disease is also an independent risk factor for retinopathy and early elevation of albuminuria in young people with T1D.[55,56]

In the TODAY2 study the major risk factors for microvascular complications in youth-onset T2D included BMI, insulin resistance, hypertension, and dyslipidemia.[16]

4 | DIABETIC KIDNEY DISEASE

Kidney complications are a major cause of morbidity and mortality among young adults with T1D. In their absence, mortality is similar to that in the general population, whereas it is significantly higher with elevated albuminuria.[57–59] The changes occurring in the kidney in individuals with T1D are generally classified into five stages, reflecting specific and progressive alterations in renal morphology and function. The earliest stage is characterized by glomerular hypertrophy, hyperfiltration and hyperperfusion. This is followed by a stage of subclinical morphological changes and increases in albumin excretion rates (AER) within the normal range.[60] Further increases in albumin excretion, with an AER between 30 and 300 mg/24 h or 20–200 μg/min in a 24-h or timed urine collection or an ACR between 3 and 30 mg/mmol (30–300 mg/g), indicate the development of moderately increased albuminuria (formerly referred to as microalbuminuria) (stage 3), which may further progress to severely increased albuminuria (formerly termed macroalbuminuria) (AER >200 μg/min or >300 mg/24 h; ACR >30 mg/mmol [>300 mg/g]) (stage 4) and, without any treatment, to kidney failure (stage 5) (Figure 1).[60,61]

CKD is defined as abnormalities of kidney structure or function, present for >3 months. CKD is now classified on Cause, GFR (G1-5) and Albuminuria category (A1-3) (KDIGO guidelines).[62] CKD, which is attributed to diabetes, is now called DKD. The prevalence of kidney failure is fortunately relatively rare in T1D.[63] In a Finnish cohort, the cumulative risk of kidney failure was 2.2% after 20 years and 7.0% after 30 years diabetes duration. The relative risk of kidney failure is as low as 0.13 (95% CI 0.08–0.22) in people diagnosed during more recent decades (2005–2011) compared to those diagnosed in 1965–1979.[64] A recent study with 50-year follow-up, however, identified kidney failure in more than 25% of the T1D population with 40 years of follow-up.[65]

Although advanced stages of DKD, such as overt proteinuria or kidney failure, are rare in children and adolescents with T1D, early structural and functional renal alterations develop soon after diagnosis of diabetes, and often progress during puberty. Rates of increased albuminuria in youth with T1D have decreased over time, likely reflecting improvements in glycemia. Data from historical cohorts,[25] such as the ORPS study, indicated a prevalence of microalbuminuria up to 26% after 10 years diabetes duration; whereas more recent studies report a prevalence between 4% and 9% after 4–8 years of diabetes duration.[11,66,67] Biopsy studies have shown that renal lesions, such as basement membrane thickening and mesangial expansion, can be detected in young normoalbuminuric individuals with T1D and these changes are predictive of subsequent albuminuria.[68]

In contrast, children and adolescents with T2D can have significant increased albuminuria at the time of diagnosis or early after diagnosis. The prevalence of increased albuminuria in a recent systematic review was 22.2% (95% CI 17.3%–27.4%).[69] Risk factors that increase the risk of non-DKD are more prevalent in adolescents with T2D, and especially in Indigenous populations,[70,71] impacted by the intergenerational effects of European colonization.[72,73] Important risk factors include exposure to diabetes in utero, the higher prevalence of obesity and immune-mediated kidney disease, such as IgA nephropathy, in Indigenous and Asian populations.[74,75] As such, many adolescents with T2D demonstrate histological findings not characteristic of DKD. In Canadian First Nation children, histologic changes include large glomeruli, focal, mild arteriolosclerosis, and focal and mild glomerular basement membrane thickening.[76]

Albuminuria has classically been considered the earliest clinical manifestation of DKD and a key risk factor for progression to proteinuria. However, 40%–50% of cases of increased albuminuria in youth with T1D can be transient or intermittent and thus not necessarily progress to more advanced stages of nephropathy.[25,77] However, as highlighted by recent studies, even if albuminuria regresses into the normal range, young people with diabetes with intermittent microalbuminuria have an increased cardio-renal risk.[25,78]

Extensive evidence indicates that increases in albumin excretion, even within the normal range, predict CVD risk in adults with T1D as well as in populations without diabetes.[79] In young people with T1D, early increases in AER can occur during the first years after diagnosis and can predict future risk of albuminuria and proteinuria.[80] In an incident cohort of childhood-onset T1D, after 6 years duration, early elevation of AER (>7.5 μg/min) was detected in 5% of children younger than 11 years and 25% of those older than 11 years. Comparing children before and after puberty, it was present in 5% compared to 26%.[81] There has been no secular reduction in AER or albuminuria in the same cohort that has shown a reduction in retinopathy: 24%–22% in the short duration cohort (2– < 5 years duration)[81]; and 45%–30% in the cohorts with median duration of 8.6 years.[3] Similar results have been reported in a study from Bangladesh.[82] The Adolescent T1D cardio-renal Intervention Trial (AdDIT) study showed that adolescents aged 10–16 years with increased urinary albumin excretion levels (upper tertile of the normal range) were at higher risk of developing not only elevated albuminuria but also had increased CVD risk, as indicated by higher carotid-intima media thickness, systolic BP, and high-sensitivity C-reactive protein levels, and higher risk of retinopathy progression.[83–85]

4.1 | Screening for albuminuria and abnormal eGFR

Albuminuria is one of the first markers of DKD.[61] Previously, ISPAD used sex-based criteria to define increased albuminuria. However, to align with international expert guideline recommendations,[62] a uniform definition of values ≥30 mg/g or 3 mg/mmol is now recommended.

Assessing ACR in a spot urine sample is the easiest method to carry out in an office setting and it generally provides accurate

information. First-voided urine in the morning is preferable because of the known diurnal variation in albumin excretion and postural effects. A random sample can be used but one should be aware that this is associated with an increased risk of false positive results. An abnormal screening value should be confirmed with at least one first morning urine collections. Timed overnight or 24-h collections are more burdensome and add little to prediction or accuracy.[86]

Confounding factors to be considered when screening for albuminuria include strenuous exercise, heat stress, urinary infections, kidney disease (i.e., IgA nephropathy or other types of nephritis, marked hyperglycemia, fever, and menstrual bleeding). All these factors can lead to elevated albuminuria.

Increased albuminuria is confirmed by finding 2 or all of 3 samples abnormal over a 3–6 month period. Persistently increased albuminuria predicts progression to kidney failure[87,88] and is associated with an increased risk of macrovascular disease and mortality.[79]

Regular follow-up is important to identify rapid or slow progression to albuminuria, as well as cases of regression to normoalbuminuria. Regular longitudinal follow-up of albuminuria is also important to identify young people with diabetes with progressive small increases of albuminuria within the normal range, which might be a prelude to the development of elevated albuminuria (previously "microalbuminuria").

It is also important to note that DKD can occur in the absence of increased albuminuria. Epidemiological studies suggest wide heterogeneity of DKD in T1D. For example, early progressive renal decline, defined as annual eGFR loss ≥3.3%, may precede the onset of microalbuminuria and its progression to macroalbuminuria.[89] Additionally, CKD in the absence of albuminuria is prevalent in people with T1D, supporting distinct pathways of DKD in T1D, including albuminuric CKD and normoalbuminuric CKD.[90] In fact, up to one-third of all cases of microalbuminuria (moderately elevated albuminuria) are known to regress to normoalbuminuria.[91] Therefore, the absence of albuminuria in a patient does not preclude DKD.

As albuminuria is not the only indicator of DKD, evaluation of kidney function is also important. Regular monitoring of eGFR is important to detect both declining kidney function and hyperfiltration, a potentially important risk factor early in the disease course. There are unfortunately limited studies that have evaluated the validity of eGFR equations in children with diabetes. Existing creatinine-based formulas have been shown to have poor agreement with urine creatinine clearance.[92] One study recently showed that the new sex-dependent CKiD equation[93] performed best in 53 children with T1D with respect to bias, precision and accuracy, compared with measured iohexol-based GFR.[94] The iCARE eGFR equation was developed and validated in Canadian First Nation children[95] with T2D, but warrants validation in additional cohorts, as well in those with T1D.

4.2 | Antihypertensive treatment for prevention of nephropathy

Effective antihypertensive therapy in young people with diabetes and nephropathy prolongs the time to ESKD.[96,97] A recent prospective study has shown further improvement in prognosis with preservation of renal function in those diagnosed with nephropathy after 2000, associated with better control of BP, greater use of renin-angiotensin aldosterone system (RAAS) inhibition, better control of lipids and glycemia and less smoking.[98]

In adults, ACE Inhibitors and ARBs reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria.[99,100] A systematic review and meta-analysis showed that in individuals with diabetes, only ACE inhibitors can prevent the doubling of serum creatinine compared to placebo.[101] In addition, in placebo-controlled studies, only ACE inhibitors (at the maximum tolerable dose) significantly reduced the risk of all-cause mortality.[102] Inhibitors of the RAAS slow progression of established advanced DKD, but the Renin Angiotensin System Study (RASS) demonstrated that RAAS blockade does not prevent the histologic or clinical features of DKD in early T1D.[103] A meta-analysis including trials comparing RAS blockers versus other antihypertensive agents in people with diabetes (and largely without albuminuria or proteinuria) did not show any superior effect of RAS blocker for the prevention of renal and cardiovascular outcomes, and suggest that that any class of antihypertensive agents can be used in people with diabetes especially in those without renal impairment.[104]

Despite the above evidence mainly from adult studies, there are still some concerns regarding the use of ACE Inhibitors in protecting long-term kidney function in young people without hypertension. In a meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria.[105] Young people with albuminuria would potentially be taking ACE inhibitors for decades. Side effects include cough, hyperkalemia, headache and impotence.[106,107] A key safety issue related to the use of ACE Inhibitors, as well as to ARBs, is the potential risk of congenital malformation when used during pregnancy. A 2012 systematic review has highlighted that fetal exposure to ACE inhibitors or ARBs has serious neonatal and long-term complications and recommended to improve awareness of these potential deleterious effects.[108] Therefore, when starting treatment with these drugs in adolescent girls, they must be made aware of this risk and contraception counseling must be provided.

Recent data from AdDIT, where 443 adolescents were randomized to treatment with an ACE inhibitor (Quinapril, 5 mg), a statin (Atorvastatin, 10 mg), a combination of both or placebo using a 2-by-2 factorial design, indicated that treatment with ACE inhibitors over 2–4 years in adolescents with T1D deemed to be at risk of complication based on their ACR in the upper tertile of the normal range is safe, with only few reported side effects, mainly hypotension (requiring dose reduction). Treatment with ACE inhibitors in this group did not have any significant effect on the primary outcome measure (change in area under the curve of $\log_{10}$ACR), but was associated with a 43% decrease in the secondary outcome, cumulative incidence of microalbuminuria during the 2–4 year treatment period, although this did not reach statistical significance.[109]

Sodium glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RA) are highly effective next

generation therapies that are already changing management of T2D.[110–113] These drugs have shown significant protective benefits with respect to progression of CKD[111] in at least 3 large RCTs. International guidelines for the management of adults with DKD now recommend SGLT2 inhibitors as first line therapies.[62] At this point they have not been approved for use in children; however, several trials are currently underway and their guidance will be available at the time of the next guideline.

5 | DIABETIC RETINOPATHY

DR is a progressive, potentially sight threatening disease of the retinal neuro-vasculature. Duration of diabetes, suboptimal glycemia, high BP and albuminuria are known risk factors contributing to the development of DR.[3,85,114,115] DR was defined and classified according to the International Clinical Diabetic Retinopathy Disease Severity Scale by Wilkinson et al.[116]

NPDR is characterized by microaneurysms, retinal hemorrhages (both pre- and intra-retinal), cotton wool spots related to ischemia and microinfarction, hard exudates due to protein and lipid leakage, intraretinal microvascular abnormalities (IRMAs) and venular dilatation and tortuosity. Mild (microaneurysms only) and moderate stages of NPDR are not vision-threatening and do not invariably progress to more severe stages of retinopathy.[117,118]

Severe NPDR (previously known as pre-proliferative) is characterized by vascular obstruction, increase in number of retinal hemorrhages and microaneurysms, IRMAs, marked venous abnormalities, and ischemia and infarctions of the retinal nerve fibers causing cotton wool spots.

Proliferative diabetic retinopathy (PDR) is characterized by neovascularisation in the retina and/or vitreous posterior surface. This can result in vision threatening events such as vessels rupturing with bleeding into the vitreoretinal space; and/or fibrosis and contraction resulting in traction retinal detachment, which can cause irreversible blindness.

DME/maculopathy is characterized by decreased vascular competence (increased vascular permeability) and microaneurysm formation, which produce exudation and swelling in the central retina.

The prevalence of any form of DR is variable in several studies and NPDR is common in children and adolescents with T1D.[119–121] Recent data from 156,090 individuals with T1D aged 10–21 years old (median T1D duration 5.2 years) from 11 countries showed an unadjusted prevalence of any DR of 5.8%. The variation across countries was 0%–16.2% with <1% youth having severe retinopathy. Four national registries reported rates >10%.[122]

Although the progression may be rapid, especially in those with suboptimal glycemia,[3,117,120,121,123] regression of DR can also occur with improved HbA1c levels.[124,125] Adolescents have a higher risk of progression to vision threatening stages of DR (severe NPDR or worse and/or DME) compared to adults with diabetes.[126] Hence, adolescence is the time when efforts should be directed to screening for early signs of DR and identification of modifiable risk factors. Regular screening for DR has reduced the proportion of blindness due to diabetes.[127]

In the UK a national screening program was introduced from 2002 with the initial age of screening starting at 12 years, because there were no reports of vision-threatening DR before this age.[128] Data from 2125 adolescents screened at age 12–13 years showed referral DR rates of less than 20%, but of these, three individuals with short duration (<5 years) required fast track referral for moderate to severe DR. At subsequent five-year follow-up, progression to vision-threatening DR had occurred in 9% of adolescents diagnosed before age 5 years and in 3% diagnosed at age 5–7 years.[128] A recent study in 662 young people with T1D in Bangladesh showed that 6.6% had DR.[119]

Several reports have found low rates of referral for DR screening in pediatric diabetes clinics.[123,124] In the T1D Exchange Registry in the US, less than 1% of 12,235 young people with diabetes reported treatment for DR at a mean age of 12 years and duration of 5 years, although this is likely to under-report the actual prevalence since the data were based on self-reported DR and only cases requiring treatment.[125]

Conversely insurance claims data show markedly higher rates reported by optometrists or ophthalmologists in a large US managed-care network: 20% of 2240 youth had developed DR at a median duration of 3.2 years with an incident rate of 52.3 per 1000 person-years; estimated to be 25% at 5 years duration. Severe DR or DME were present in 2% and the youngest patient with PDR was 6 years old. Lower rates of screening uptake were found in those with lower family income and this group had higher rates of DR, suggesting that the actual rate may be even higher.[127]

Initial worsening of DR can occur with improvement in HbA1c as occurred in the DCCT, but such worsening did not result in clinically significant visual loss when detected and managed appropriately and, over time, intensive insulin therapy continued to be superior to standard therapy.[129] This initial worsening of DR associated with improved glycemia also occurred in young people with diabetes with growth failure due to severe under-insulinization.[130] However within 1.5–3 years, the advantage of intensive treatment is evident.[129]

Pregnancy is a recognized risk factor for acceleration and progression of DR[131,132]; hence screening should be undertaken preconception, every trimester, and 1 year postpartum.

5.1 | Assessment of retinopathy

The most sensitive detection methods for DR screening are a clinical bio-microscopic fundus slit-lamp examination through dilated pupils by an ophthalmologist or optometrist and mydriatic 7-field stereoscopic retinal photography. The latter is optimal for research but not often available in the clinical setting where, instead, mydriatic and nonmydriatic 2-field fundal photography is often used for screening. Other methods are direct ophthalmoscopy, indirect ophthalmoscopy, fundus fluorescein angiography, ultrawide-field imaging and optical coherence tomography (OCT). Fundal photography provides a

validated tool that can be useful for monitoring clinical quality and in research, but photographs may not be gradable in which case ophthalmoscopy needs to be performed; mydriasis can reduce the technical failure rate.[133] Ultrawide-field imaging may improve the detection of retinopathy and predict progression to proliferative retinopathy.[134] Fluorescein angiography reveals functional vascular abnormalities (vascular permeability) as well as structural abnormalities in the blood vessels, whereas OCT reveals only structural abnormalities, specifically DME and other anomalies including loss of the various layers of the neural retina. The newer technique of optical coherence tomography angiography (OCTA) is promising due to the possibility to detect disturbances in retinal vessel density, foveal thickness and foveal avascular zone, which are predictive for future DR occurrence and severity. Alterations in retinal vessel density occur early before the onset of clinically detectable other diabetes-related complications, which may contribute greatly to the early detection of DR.[135,136]

When an incident cohort of children diagnosed in 1990–1992, with a median HbA1c of 8.7%, was examined for DR after 6 years diabetes duration, the relative effects of age and puberty could be compared. Early DR, defined as one microaneurysm or hemorrhage, was present in 24% of the study population. DR was present in 8% of children younger than 11 years of age and 25% of those 11 years old or older; and when comparing prepubertal versus pubertal children, it was present in 12% versus 29%.[29]

More recent data using the same methods in mid-adolescence (median age 16.4 years) with minimum duration of 5 years demonstrated that DR declined from 53% (in 1990–1994) to 23% (in 2000–2004) and then to 12% (in 2005–2009).[3] This reduction has not been sustained at the same referral clinic in Australia, with the rate being 21% in the decade 2000–2009 and 20% in 2010–2019.[137] In a younger population with T1D (median age 14.5 years, duration 2–5 years), the prevalence of mild background retinopathy declined from 16% in 1990–1994 to 7% in 2003–2006.[81] Furthermore, those with shorter duration had considerably less DR, and retinopathy was present in only 6% of the youngest group (aged 11–13 years). Moderately severe DR was only found in those with diabetes duration greater than 10 years[137]; and nine cases of sight-threatening retinopathy were found in the last decade.[138] The prevalence of DME in youth with T1D was 0.9% in the last decade.[137]

The DCCT/EDIC study group has reviewed optimal frequency for rescreening for DR, and recommends repeat screening at intervals, which varies, based on the baseline DR status and HbA1c in adults with T1D.[139] Whilst the participants in that study consented to randomization to intensive therapy or standard therapy for the DCCT, a free-living observational cohort of adolescents in Australia, also demonstrated that screening could be extended to 3 years if no DR was present with less than 1% chance of progression to moderately severeDR.[140]

For adolescents with T2D, the TODAY follow-up study shows a worrying increase in DR over 7 years. At the second assessment in 2017–2018, 51% of participants had retinopathy compared to 13% in 2010–11. Their mean age was 24 years and duration 11 years: 9% had moderate to severe DR and 3.5% had DME.[16]

5.2 | Specific treatment for DR

Once sight-threatening DR is detected, treatment options include laser photocoagulation and/or anti-VEGF therapy.[117,141] Panretinal laser photocoagulation (PRP), commonly known as "laser therapy," consists of multiple discrete outer retinal burns throughout the mid and far peripheral area but sparing the central macula. It has been proven to reduce the progression of visual loss by more than 50% in young people with PDR.[142,143] However, photocoagulation is not indicated for mild or moderate NPDR.[144] Side effects of treatment are decreased night and peripheral vision and subtle changes in color perception. Complications of laser therapy include vitreous hemorrhage, choroidal neovascularisation or detachments and visual sequelae of misplaced burns.

For PDR, intravitreal injection of antiVEGF (ranibizumab, aflibercept, and bevacizumab) is now increasingly used and show better 12-month results for visual acuity than PRP.[145] This treatment is not destructive but does require repeated visits and injections for efficacy, (e.g., monthly injections for the first 5 months with up to nine injections in the first year); and carries the rare risk of ocular infection.[145] In the DRCR network Protocol S study at 5 years, visual acuity was similar for both the PRP and intravitreal ranibizumab groups, although eyes treated with antiVEGF had better visual fields and lower incidence of DME.[146,147]

For DME with vision loss, anti-VEGF (ranibizumab, aflibercept, and bevacizumab) is now considered standard of care and has shown superior outcomes over 5 years compared to laser treatment.[148,149] Intravitreal use of longer acting steroids (dexamethasone and fluocinolone) is an alternative to antiVEGF for DME, with a possible reduced burden of injections.[150] However, because of the inferior visual acuity results and the potential adverse effects of cataract and glaucoma development, intravitreal steroid is rarely used as first-line therapy for DME.

Surgical treatment such as vitrectomy may be indicated for persistent vitreous hemorrhage, tractional retinal detachment or extensive fibrosis.[141]

6 | DIABETIC CATARACTS

Cataracts have been reported in people with T1D close to or even preceding the diagnosis, with a prevalence between 0.7% and 3.4%.[151] Hence comprehensive initial eye examination to detect cataracts should also be considered at the time of retinopathy screening, or earlier, if there is any visual disturbance.

7 | DIABETIC NEUROPATHY IN YOUTH

The somatic and autonomic components of the peripheral nervous system (PNS) are commonly affected by both T1D and T2D in youth and adults.[152] The unique anatomy of the somatic branch of the PNS, with the cell body lying adjacent to or in the spinal cord with select nerve fibers projecting long distances to the most distal extremities, renders the PNS susceptible to shifts in energy sources, as is often present in diabetes.[153,154] Small unmyelinated nerve fibers that carry

pain and temperature perception are frequently affected first in diabetes, followed by injury to myelinated nerve fibers, which convey vibratory and position sense.[155] Weakness is a late sign and rarely present in youth.[156] The most frequent type of injury occurs in a symmetric distal to proximal gradient, known as a stocking and glove pattern, and is commonly termed diabetic neuropathy.

The reported prevalence of diabetic neuropathy in children and youth varies due to the use of different diagnostic tests,[157] and the frequent presence of subclinical neuropathy,[158] which is challenging to detect. The Pittsburgh Epidemiology of Diabetes Complications study reported a 3% prevalence of diabetic neuropathy in youth with T1D ($n = 400$) less than 18 years of age.[159] A larger EURODIAB study of individuals with T1D ($n = 3250$) found a 19% prevalence in the 15–29 year-old bracket.[160] An Australian study reported that 14% of T1D youth ($n = 819$) as young as 11–17 years-old developed diabetic neuropathy after only 2–5 years of disease duration.[81] The SEARCH for Diabetes in Youth study found diabetic neuropathy in 7% of T1D youth ($n = 1734$).[161] This variability in prevalence estimates could be attributable to the diagnostic test employed; a small study of individuals with T1D ($n = 73$) concluded that prevalence was 4% by neuropathy symptoms, 36% by abnormal neurological exam, 57% by nerve conduction abnormalities, 51% by vibration perception threshold, and 26% by tactile perception threshold.[157]

In T2D, the overall trend is for an increasing prevalence of diabetic neuropathy in recent years in parallel with the rising pediatric T2D prevalence.[162–164] The SEARCH study reported diabetic neuropathy in 22% of T2D youth ($n = 258$),[11,161] while the TODAY study reported a cumulative incidence of diabetic neuropathy of 38.5% in males and 27.2% in females.[165]

The most frequently studied autonomic neuropathy is cardiac autonomic neuropathy,[166] an independent risk factor for cardiovascular mortality.[167] The SEARCH study found early signs of cardiovascular autonomic dysfunction[168] at a similar prevalence in youth with T1D (12%) and T2D (17%).[169] A systematic review of published studies of young people with T1D (aged less than 24 years) estimated cardiac autonomic neuropathy prevalence from 16% to 75%, based on the diagnostic method.[170]

7.1 | Assessment of diabetic peripheral neuropathy in youth

Young people with diabetes initially experience burning, prickling and/or paresthesiae of their feet caused by small fiber dysfunction. Over time, large fiber involvement occurs and young people with diabetes experience numbness and, in extreme cases, poor balance due to proprioceptive loss.[152,155] While there are multiple symptom scores for adults,[155] none exist for youth.[171]

7.1.1 | Clinical examination

Physical examination should include a bedside evaluation of small fiber function, assessing temperature or pinprick sensation in the feet.[172,173] Large fiber function is assessed at the great toe with a 128 Hz tuning fork (high specificity but low sensitivity) for vibratory perception[174] and a 10 g monofilament for touch/pressure sensation.[174] Evaluation of ankle reflexes complete the assessment of large fiber function.[172,173] There are several simple clinical tools that can be used to assess diabetic neuropathy in youth.[156] The DCCT,[175] SEARCH,[161] and the TODAY[165] studies all used the Michigan Neuropathy Screening Instrument.[176]

7.1.2 | Quantitative testing

Quantitative testing is rarely required and is primarily used for research purposes. Quantitative sensory testing normative values exist for youth.[177] Other available tests include thermal discrimination testing[178] for small fiber function, and assessment of vibration for large fiber function using a biothesiometer,[157] pocket-sized Vibratip™.[179] Again, these are mostly used in research settings and age- and sex-specific normal ranges need to be applied when interpreting results.

7.1.3 | Nerve conduction studies

Nerve conduction studies are clinically useful if the presentation of diabetic neuropathy is atypical, with more evident motor than sensory symptoms and signs and/or a strong asymmetrical clinical presentation.[180–182] Normative values for nerve conduction velocities for youth are published.[183]

7.2 | Assessment of diabetic autonomic neuropathy in youth

Autonomic neuropathy can manifest in the cardiovascular, gastrointestinal, and sudomotor systems as resting state tachycardia, exercise intolerance, gastroparesis, and dysfunctional sweating responses.[152,184] Cardiovascular autonomic neuropathy may be detected by impaired HRV or BP changes in response to certain maneuvers, for example, deep breathing, standing, and Valsalva maneuver; however, cardiovascular reflex tests are the gold standard. Importantly, normative values for HRV must be consulted.[185] Autonomic neuropathy in the gastrointestinal system can be detected by gastric emptying scintigraphy, whereas in the sudomotor system, thermoregulatory sweat test and Sudoscan may be used.[186,187] These diagnostic tests are rarely used in pediatric practice.

8 | MACROVASCULAR DISEASE

CVD remains the major cause of mortality in people with T1D.[188] Individuals with T1D experience an earlier onset of cardiovascular events and a higher CVD mortality compared to their peers without

diabetes.[189] Recent data from the Swedish Diabetes Registry showed that young people diagnosed with T1D before the age of 10 years had 10-times higher risk of future acute myocardial infarction compared to those diagnosed between the ages of 26–30 years, and over 30-times higher CVD risk than the general population.[190]

In youth with T1D, overt manifestations of CVD such as angina or myocardial infarction are rare, but early subclinical signs can be detected by surrogate measures, such carotid and aortic intima-media thickness (cIMT and aIMT), pulse wave velocity, and flow mediated dilation.[191] Atherosclerosis starts in childhood and adolescence as shown by thickening of cIMT and aIMT[192–194] and silent coronary atherosclerosis measured by intravascular ultrasound in young adults with childhood onset diabetes.[195]

Suboptimal glycemia is one of the main modifiable risk factors related to early vascular abnormalities and increased risk of later CVD events.[5] However, other traditional cardiometabolic risk factors such as obesity, hypertension and dyslipidemia, renal function along with non-modifiable risk factors, such as sex and diabetes duration, and lifestyle factors, contribute to CVD risk.[5] Hypertension has a greater impact on CVD in young people with diabetes than in individuals without this condition.[40] BP control reduces cardiovascular morbidity and mortality in diabetes.[41] Cholesterol plays an important role in the initiation and progression of atherosclerosis. Well-controlled T1D is not associated with gross blood lipid disturbances, but changes in lipoprotein subclasses can be detected.[44] In contrast, youth with suboptimal HbA1c concentrations have a more atherogenic lipid profile than youth without diabetes, with a positive association between HbA1c and increased levels of total cholesterol, LDL-cholesterol, non-HDL cholesterol and triglycerides.[42,196–198] Adolescents with T1D also show higher levels of apolipoprotein B (apoB) compared to their peers without diabetes, regardless of HbA1c levels.[197] Studies in adults and adolescents with T1D suggest a possible complementary role for measurement of apoB in addition to screening LDL-cholesterol. However, current data are insufficient to warrant the addition of apoB screening to current lipid screening guidelines for youth with diabetes. Changes in lipids associated with increased cardiovascular risk are also associated with central obesity in T1D as well as T2D.[199]

A high BMI is associated with increased rates of CVD events and mortality in adults with T1D.[200] Overweight and obesity are common among youth with T1D, with rates of 9%–20%, and are associated with higher LDL-cholesterol and triglycerides, and lower HDL-cholesterol concentrations.[201,202]

Insulin resistance is another well-known CVD risk factor, which is common among adolescents with T1D.[203] In adults with T1D, risk of CVD and related mortality increases with the presence and severity of DKD.[204] Recent data from cohorts of adolescents with T1D have confirmed the value of AER as an early marker of vascular complications.[84,205] In the AdDIT study, an albumin-creatinine ratio (ACR) in the top tertile of the population distribution was associated with greater cIMT, and flow-mediated dilation and BP.[84]

Lifestyle factors can also contribute to CVD. These include smoking, alcohol, sedentary lifestyle, and stress.[189] In a recent study, 10% of youth with T1D reported alcohol consumption, 10% cigarette smoking and 6% both alcohol and cigarette use.[206] Compared to non-drinker and non-smoker youth, smokers showed significantly higher percentages of CVD risk factors. In a cohort of adolescents with T1D, those achieving 4–6 of the goals of Screening Guidelines had better surrogate markers of macrovascular disease than those achieving less and have comparable results to nondiabetic controls.[207]

8.1 | Management of hypertension

Hypertension in children and adolescents (<13 years) is defined as BP equal to or above the 95th percentile for age, sex and height, whereas in older adolescents (age ≥13 years) it is defined as SBP ≥130 and/or DBP ≥80 mmHg. Elevated BP (previously known as "prehypertension") is defined as BP ≥90th percentile for age, sex, and height, or from the age of 13 years as BP between 120 and 129/80 mmHg.[208] Similarly to overt hypertension, elevated BP is associated with adult hypertension.[209,210]

Children and adolescents with elevated BP or hypertension should have elevated BP confirmed on three separate days. Confirmation of hypertension is recommended by 24-h ambulatory BP measurements (ABPM). Normative ABPM values are available and should be used to interpret the results.[211]

In children and adolescents with elevated BP, initial treatment includes lifestyle interventions, including DASH diet and moderate to vigorous physical activity at least 3–5 days per week (30–60 min per session).[209,212,213] If target BP is not reached within 6 months of initiating lifestyle intervention and pharmacologic treatment should be started.

When hypertension is confirmed in children and adolescents with T1D, in addition to lifestyle modification, pharmacologic treatment should be considered.[208] Pharmacologic treatment of hypertension in children and adolescents should be initiated with an angiotensin converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), long-acting calcium channel blocker, or a thiazide diuretic. ACE inhibitors are recommended for use in children and adolescents with hypertension and/or albuminuria, but an ARB can be used if the ACE inhibitor is not tolerated (e.g., due to cough).[208] They have been effective and safe in children in short-term studies.[109,214,215] Reproductive counseling and implementation of effective birth control is required when treatment is initiated due to the potential teratogenic effects of both drug classes. The goal of treatment is BP consistently <90th percentile for age, sex, and height.

8.2 | Management of dyslipidemia

Screening for dyslipidemia should commence from 11 years of age in youth with T1D. If there is a family history of either hypercholesterolemia or early cardiovascular death, screening should be commenced earlier from age 2 years. It is appropriate to screen with a non-fasting blood lipid profile; if this is abnormal (i.e., triglycerides or LDL levels are elevated), then a fasting profile should be performed.[216,217] Data

from the NHANES III study suggest that non-fasting lipids screening has good prognostic value[216] but data in young people with diabetes are lacking.[217] Fasting lipids are also indicated for young people with diabetes receiving treatment for dyslipidemia.

High LDL-cholesterol is defined as values >2.6 mmol/L (100 mg/dL).[218] If this is present then interventions to improve glycemia, dietary changes and increased exercise should be the first approach to management. Dietary changes restrict saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day.[219]

Previous studies have reported that a 6-month dietician-led program prioritizing a Mediterranean-style diet improved levels of LDL-C and non-HDL-C. Another 6-month trial evaluating the effect of a supervised exercise program showed improvements in dyslipidemia.[220,221] Improved glucose control has been associated with a more favorable lipid profile but may be insufficient to completely restore normal lipid levels.[196]

If the implementation of lifestyle interventions for 6 months does not lower LDL-cholesterol to <3.4 mmol/L (130 mg/dL), statins should be considered in children aged >10 years, with an ideal target of LDL cholesterol <2.6 mmol/L (100 mg/dL). In adults with diabetes, statins are effective in the primary and secondary prevention of major cardiovascular events, including vascular mortality, stroke and limb and coronary revascularization.[222,223] Short-term trials, mainly in the context of familial hypercholesterolemia, have shown that simvastatin, lovastatin and pravastatin are effective and safe in children and adolescents.[224–226] No significant side effects were observed in terms of growth, pubertal progression, endocrine function parameters, or liver or muscle enzymes.[224–226] The AdDIT trial confirmed the efficacy and safety of statin therapy (atorvastatin) in adolescents with T1D treated for a 2–4 year period.[109] In the AdDIT trial, atorvastatin use was associated with a decreased in total, LDL and non-HDL cholesterol levels as well as in an improved ratio of the apolipoprotein B/apolipoprotein A ratio; however, statin treatment did not lead to any improvement in cIMT or FMD.[109,227]

CONFLICT OF INTEREST

PB has acted as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Sanofi, Novo Nordisk and Horizon Pharma. PB serves on the advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk and XORTX. RPW has research support from Dexcom, Eli Lilly & Co and Tandem Diabetes Care. RPW has served on an advisory board for Dompe.

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How to cite this article: Bjornstad P, Dart A, Donaghue KC, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Microvascular and macrovascular complications in children and adolescents with diabetes. *Pediatr Diabetes*. 2022;23(8):1432-1450. doi:10.1111/pedi.13444

DOI: 10.1111/pedi.13445

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Other complications and associated conditions in children and adolescents with type 1 diabetes

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KEYWORDS: autoimmune comorbidities, bone health, celiac disease, growth and development, skin disorders, thyroid, type 1 diabetes

1 | WHAT IS NEW OR DIFFERENT

- Revised recommendations for celiac disease (CD) screening and biopsy that include consideration of a serology-based diagnostic approach.
- Expanded section on skin disorders that includes continuous glucose monitoring (CGM)-related and insulin pump-related skin issues.
- Updated section on bone health with general recommendations regarding optimization of bone health in youth with type 1 diabetes (T1D).

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Regular monitoring of anthropometric measurements and physical development, using growth and body mass index (BMI) standards, are essential in the continuous care of children and adolescents with T1D. **E**
- Screening for thyroid disease by measurement of TSH, anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies is recommended soon after diagnosis of diabetes once the individual is clinically stable. **B**
  Thereafter, TSH should be measured every second year in asymptomatic individuals and every year in individuals with positive antibodies at diagnosis or a family history of autoimmune thyroid disease. **E** TSH should be measured sooner with the presence of clinical signs or symptoms of thyroid disease, including goiter or growth impairment. **E**
- CD may present with varied clinical signs and symptoms that may be gastrointestinal (diarrhea, nausea, abdominal pain), extra intestinal (unexplained weight loss, iron deficiency anemia, decreased bone mineralization, aphthous stomatitis) or diabetes-related (unexplained hypoglycemia). The process of active case finding on the basis of symptoms can be challenging as CD is frequently asymptomatic in children and young adults with T1D. **B**
  - Screening for CD is recommended during the initial year of diabetes diagnosis and at 2–5 years intervals. **C**

More frequent assessment is indicated if the clinical situation suggests the possibility of symptomatic CD or the child has a first-degree relative with CD. Clinical signs and symptoms of CD or the availability of blood testing for other reasons may necessitate screening for CD at the time of diabetes diagnosis, but clinicians should consider the potential challenges for children and families in managing new onset diabetes plus CD in asymptomatic cases and defer screening after the period of initial diagnosis. **E**

- Measurement of human leukocyte antigen (HLA)-DQ2 and DQ8 is rarely helpful to exclude CD in individuals with T1D and is not recommended as a screening test. **B**
- Screening for IgA deficiency should be performed at the time of CD screening. In individuals with diabetes with confirmed IgA deficiency (low total IgA concentrations), screening for CD should be performed using an IgG-based specific antibody tests (tissue transglutaminase (TTG-IgG) or endomysial antibody (EmA-IgG) or both). **B**

  All IgA deficient individual with diabetes who are positive for an IgG-based serological test should be referred to a pediatric gastroenterologist for biopsy. **C**
- In children with normal IgA levels, use of TTG-IgA as an initial screening test, with levels exceeding ≥10 times the upper limit of the TTG-IgA assay with confirmation of positive EmA-IgA in a second blood sample while on a diet containing gluten can be used to diagnose CD, as suggested by recent European guidelines. Only antibody tests with calibrator curve-based calculation and having the TTG-IgA ≥10 times the upper limit value within their measurement range, should be used. It is recognized that this approach has not been universally adopted as standard of care internationally. **E**
- In the symptomatic child, a biopsy-sparing approach may be considered on a case-by-case basis in consultation with a pediatric gastroenterologist and the child and family with initiation of a gluten-free diet with resolution of symptoms. **E**
- In the asymptomatic child, evidence for a biopsy-sparing approach is limited in children with T1D and was not addressed by recent European guidelines. The implications of a life-long commitment to be on a gluten-free diet in an individual with both CD and diabetes without symptoms is an important consideration and the decision to perform duodenal biopsies for confirmation of gastrointestinal pathology should also be discussed with parents and the child. **E**
- Upon confirmation of the diagnosis of CD, they should receive educational support from an experienced pediatric dietitian with knowledge of the gluten-free diet (GFD) and both individuals with diabetes and their diabetes care team should be vigilant as insulin requirements may change during transition to the GFD. **E**
- Children with CD should have annual screening for thyroid function and monitoring of vitamin D to optimize bone health. **E**

- Diabetes care providers should be alert for symptoms and signs of other autoimmune diseases in children and adolescents with T1D including Addison's disease, autoimmune gastritis, juvenile idiopathic arthritis (JIA), other gastrointestinal diseases (e.g., Crohn's disease, ulcerative colitis, autoimmune hepatitis), although these are rare. **E**

  Individuals with T1D and adrenal disease might have a greater risk of mortality; therefore, these individuals require additional vigilance to optimize metabolic outcomes, to reduce hypoglycemia and diabetic ketoacidosis and to prevent adrenal crises. **E**
- Routine clinical examination should be undertaken for skin and joint changes. Regular screening by laboratory or radiological methods is not recommended. **E**

  Education regarding proper injection technique, rotation of injection sites with each injection and non-reuse of needles remains the best strategies to prevent lipohypertrophy (LH) and lipoatrophy (LA). **E**
  - Injection sites should be regularly assessed at each clinic visit for LH and LA as they are potential causes of glucose variability. **C**
  - Routine clinical examination for skin irritation should be performed in children and adolescents using insulin pumps and/or CGM. Rotation of pump and sensor insertion sites is recommended. **E**
- Screening for vitamin D deficiency, particularly in high-risk groups (CD, darker skin pigmentation) should be considered in young people with T1D and treated using appropriate guidelines. **E**
- Impaired bone health is an emerging long-term complication of T1D. Individuals with diabetes should be counselled to optimize calcium and vitamin D intake, avoid smoking, and perform regular weight-bearing exercise. Individualized assessments of bone health may be considered in children with medical co-morbidities such as CD or a family history of early osteoporosis. **E**

3 | GROWTH, WEIGHT GAIN AND PUBERTAL DEVELOPMENT

Monitoring of anthropometric measurements and physical development, using age-appropriate standards and taking mid-parental height into account, is a crucial element in the care of children and adolescents with diabetes (Table 1).

Larger body size and rapid growth, with greater height velocity, prior to and at diagnosis of T1D has been reported.[1–5] The precise mechanism for this and whether or not this increased height is maintained is unclear; however, factors in children who are autoantibody positive, a sustained increased BMI is associated with an increased risk of progression to T1D[6,7] and high BMI has been identified as a risk factor for islet autoimmunity and subsequent development of T1D[8,9]; however not all reports confirm this.[10]

There is considerable evidence that youth with suboptimal glycemic management show a decrease in height velocity, whilst better-managed youth with diabetes maintain normal rates of growth.[11] Insulin is a major regulator of the growth hormone (GH) and insulin like growth factor-1 (IGF-1) axis; adequate insulin secretion and

normal portal insulin concentrations are needed to maintain normal serum concentrations of IGF-1 and insulin like growth factor binding proteins, and to promote growth.[12,13] The use of multiple daily insulin injection regimens, insulin analogs, and new technologies, including insulin pumps and CGM, have led to more physiological circulating insulin concentrations, thus improving GH/IGF-1 concentrations and height outcomes, independent of glycemic status.[12] The negative effect of elevated HbA1c on growth appears to be exacerbated during puberty, a time of physiological insulin resistance.[14] Significant impairment in growth during puberty has also been reported particularly in young people who develop albuminuria.[15] In most youth with T1D, modern diabetes management using insulin pump or >3 injections daily is associated with normal growth.[16,17] Mauriac syndrome, characterized by growth failure, hepatomegaly with glycogenic hepatopathy and steatosis, and late pubertal development is an uncommon complication in children with persistently elevated HbA1c; however new cases continue to be reported.[18,19] Insulin insufficiency, CD and other gastrointestinal disorders should also be considered in these cases. Recently, a mutation in an enzyme involved in glycogen metabolism (catalytic subunit of glycogen phosphorylase kinase) was reported in a case of Mauriac syndrome that increased glycogen deposition in the liver. The postulated mechanism is that this mutant enzyme combines with hyperglycemia to directly inhibit glycogen phosphorylase activity, resulting in many of the phenotypic features observed in this syndrome.[20]

Once the child or adolescent has regained weight after the initial diagnosis of T1D, excessive weight gain may indicate high-energy intake, which may be related to excessive exogenous insulin. Excessive weight gain is more common during and after puberty, especially in girls, as well as in those whose diabetes was diagnosed during puberty.[21] Historically, The Diabetes Control and Complications Trial and other studies reported increased weight gain as a side effect of improved glycemic management with intensive insulin therapy, potentially related to the impact of recurrent hypoglycemia.[21,22] Children with obesity and T1D have a higher prevalence of cardiovascular risk factors (hypertension, dyslipidemia and cardiac autonomic dysfunction) than normal weight children with T1D.[23,24] Recent data from multiple international registries show higher rates of overweight and obesity in children and adolescents with T1D, compared to their peers without diabetes.

Therefore, careful monitoring based on BMI-charts for age and gender and management of weight gain should be emphasized in diabetes care as obesity is a modifiable cardiovascular risk factor.[25–27] There is a complex interplay among age, puberty, insulin requirement, metabolic status and BMI.[28] Use of adjunctive therapy with insulin sensitizing agents, such as the addition of metformin along with insulin does not improve glycemic outcomes in overweight adolescents with T1D; however, it may lead to decreased insulin requirements and a reduction of BMI.[29]

Girls with T1D are at increased risk of being overweight[21] and clinicians must also be aware that these weight changes are recognized risk factor for later development of eating disorders.[30–32] In association with increased weight, there is also the risk of ovarian hyperandrogenism, hirsutism and polycystic ovarian syndrome in girls with T1D.[33,34] In a recent study of adolescents with hyperandrogenism and T1D, metformin treatment significantly decreased serum androgen concentrations compared to placebo but did not significantly affect clinical parameters, such as hirsutism, ovulation and glycemic status. Therapy for only 9 months, however, is generally thought to be insufficient to impact hirsutism.[35,36] Increased doses of insulin are usually required during puberty and it is important to reduce insulin doses after pubertal development is completed and insulin resistance has decreased.

Risk of delayed menarche and menstrual irregularities together with hyperandrogenism are increased in youth who develop T1D before the onset of puberty, and several studies indicate that the delay is independent of glycemic management.[37–39] A recent study indicated delayed menarche and earlier menopause in females with T1D resulting in a shorter reproductive period in females with T1D, which may affect reproductive health and requires additional research.[40]

4 | ASSOCIATED AUTOIMMUNE CONDITIONS

Children with T1D are at increased risk for comorbid autoimmune diseases and clinicians must be aware of the symptoms and risk factors associated with common comorbid autoimmune diseases. A high proportion of children and adolescents with T1D have detectable organ-specific autoantibodies (e.g., thyroid, CD) in addition to islet autoantibodies, and approximately 25% of individuals with T1D are diagnosed with another autoimmune disease.[41–44] Comorbid autoimmune diseases occur more commonly in females compared to males and the incidence increases with age.[41] In situations where laboratory testing is not available or is cost prohibitive, the clinician must rely on careful monitoring of linear growth and relevant symptoms. Screening at regular intervals for common comorbid conditions (autoimmune thyroid disease [AITD] and CD), which may be subclinical or asymptomatic, allows for earlier identification and treatment.

Autoimmune thyroid disease (AITD) is the most common comorbid autoimmune condition seen in T1D followed by CD.[41] Other autoimmune conditions that occur less commonly in youth with T1D include primary adrenal insufficiency, collagen vascular disease (e.g., rheumatoid arthritis, lupus erythematosus, psoriasis, scleroderma), other gastrointestinal diseases (e.g., Crohn's disease, ulcerative colitis, autoimmune hepatitis, autoimmune gastritis), and skin diseases (e.g., vitiligo, scleroderma). Rare cases of multiple sclerosis have been reported in association with T1D in childhood and adolescence and will not be described in detail.[45,46]

4.1 | Hypothyroidism/Hashimoto thyroiditis

Thyroid disease occurs more frequently in children and adults with T1D than in the general population. The incidence of AITD in children and adolescents ranges from 0.3 to 1.1 per 100 patient years and prevalence is approximately 3%–8% of children with T1D.[47,48] The

prevalence of AITD increases with age to approximately 20%; most have hypothyroidism.[41] Anti-thyroid antibodies can be detected in up to 29% of individuals soon after diagnosis with T1D and are strongly predictive for the development for AITD, mostly hypothyroidism.[42,48,49] Anti-thyroid antibodies are observed more frequently in girls than in boys and are associated with age, diabetes duration and pubertal maturity.[50] In addition, the presence of islet autoantibodies to GAD (Glutamic Acid Decarboxylase) and ZnT8 (Zinc Transporter-8) are associated with thyroid autoimmunity.[43,51] Screening children for anti-thyroid antibodies (antithyroid peroxidase and antithyroglobulin) can help stratify which youth with diabetes to follow most closely for development of hypothyroidism.

Clinical features of hypothyroidism include the presence of a painless goiter, decreased linear growth, fatigue, cold intolerance, bradycardia and weight gain. Glycemic management may not be significantly affected, but hypoglycemia has been linked to hypothyroidism.[52]

Overt hypothyroidism is confirmed by demonstrating a low free T4 level and a raised thyroid stimulating hormone (TSH) concentration. Importantly, thyroid function tests can be misleading (euthyroid sick syndrome) if an individual with diabetes is not metabolically stable (e.g., after diabetic ketoacidosis) or has suboptimal blood glucose management.[53,54] In thyroid autoantibody positive, asymptomatic individuals, compensated (subclinical) hypothyroidism may also be observed, with normal free T4 and mildly increased TSH levels.

Treatment of hypothyroidism in T1D is the same as that used in the general population and is based on replacement with oral levothyroxine (synthetic T4) to normalize TSH levels. This may allow for regression of goiter if present. In addition to routine monitoring of TSH levels, management of treated thyroid disease should include measurement of thyroid function tests after changing levothyroxine dosage. It is important to note that untreated hypothyroidism can worsen total cholesterol, LDL cholesterol and triglyceride levels.[55] Children should also have their thyroid gland palpated yearly for the development of nodules or cysts that would require further evaluation.

4.2 | Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with T1D, but is still more common than in the general population. The reported prevalence of hyperthyroidism ranges from 0.5% to 6%, with the highest rates reported in children.[41,48,56,57] Hyperthyroidism may be due to Graves' disease or the hyperthyroid phase of Hashimoto's thyroiditis, sometimes referred to as Hashitoxicosis.

Hyperthyroidism is characterized by weight loss, increase in appetite, palpitations, tachycardia, tremors, hyperactivity, difficulty concentrating, heat intolerance and thyroid enlargement. Characteristic eye findings such as exophthalmos and lid lag may or may not be present in children but are often milder than in adults.[58] Hyperthyroidism is confirmed with a suppressed TSH level and an elevation of one or more measures of thyroid hormone (Free T4 and/or Free T3). Graves' disease is confirmed by the presence of TSH receptor antibodies.

Hyperthyroidism is treated with the anti-thyroid drug carbimazole or methimazole; which is the recommended treatment in children due to the increased risk of liver failure with propylthiouracil treatment.[59] Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to manage tachycardia and agitation. If people with diabetes do not go into remission or cannot be managed on antithyroid medications, definitive treatment options include thyroidectomy or ablation with radioactive iodine.[60]

4.3 | Celiac disease

The prevalence of CD ranges from 1%–16.4% among children and adolescents with T1D.[61–64] An international comparison study that included 53,000 children and adolescents with T1D across three continents reported a prevalence of biopsy proven CD of 3.5%, with rates ranging from 1.9% in the U.S. to 7.7% in Australia.[61] A recent report of the SWEET registry reported a mean prevalence of 4.5% with rates ranging from 1.9% in Asia/Middle East to 6.9% in Australia/New Zealand[64]; however these data may not be fully reflective of high rates of CD from other clinic- and population-based studies showing high rates of CD in the Middle East and Indian subcontinent.[65,66]

The risk of CD is inversely and independently associated with age at diagnosis of diabetes, with the greatest risk in those with diabetes diagnosed before 5 years of age.[62,67–69] This association is common to both genders. The prevalence of CD increases with longer duration of diabetes.[63]

Most cases of CD are diagnosed within the first year after T1D diagnosis and youth with T1D may develop CD within the first 5–10 years after T1D diagnosis. However, it is important to appreciate that the diagnosis of CD can also be made beyond this period into adulthood.[64–66,70,71] While there may be pragmatic reasons to assess for CD at diagnosis to coincide with blood testing, consideration of CD screening in asymptomatic children may be deferred after the period of initial diagnosis, as managing both new onset diabetes and CD may be overwhelming for children and their families.

CD is often asymptomatic; i.e., not associated with gastrointestinal symptoms, poor growth and/or deterioration in glycemic status or hypoglycemia.[72–76] The presence of CD should be evaluated in any child with gastrointestinal signs or symptoms (including chronic or intermittent diarrhea and/or constipation, chronic abdominal pain/distention, flatulence, anorexia, dyspeptic symptoms), extra intestinal symptoms (including iron deficiency anemia, unexplained poor growth, weight loss, recurrent aphthous ulceration, decreased bone mineralization) or unexplained hypoglycemia.[68] It should be noted that tissue transglutaminase IgA (TTG-IgA) antibodies titers are higher in people with diabetes with gastrointestinal manifestations as compared to asymptomatic individuals.[77]

Screening for CD is based on the detection of IgA antibodies (TTG-IGA and/or EmA-IgA); both tests demonstrate sensitivity and specificity >90%.[78,79] TTG thresholds extrapolated from the general population for the diagnostic evaluation of CD may not be suitable for use in asymptomatic individuals with T1D. Higher thresholds than the

manufacturer's recommendations have been reported in individuals with asymptomatic CD.[79] Laboratories reporting CD-specific antibody test results for diagnostic use should continuously participate in quality control programs on a national or international level. The approach to use HLA-DQ2 and HLA-DQ8 as first line screening, because CD is unlikely if both haplotypes are negative, is not recommended, given the high proportion of individuals with diabetes who carry these risk alleles. Thus, the use of HLA as first line testing to screen for CD in this population is neither practical nor cost effective.[80–84]

IgA deficiency, 1:500 in the general population, is more common in people with T1D and those with CD.[85] Therefore, screening for IgA deficiency should be performed at the time of CD screening. If the child is IgA deficient, IgG-specific antibody tests (TTG IgG, EmA IgG) must be used for screening. This is important because CD may be more common in those with IgA deficiency than in the general population.[86] All individuals with diabetes who are IgA deficient and positive for an IgG based serological test should be referred to a pediatric gastroenterologist for biopsy.

In children with normal IgA levels, recent European guidelines suggest use of TTG-IgA as an initial screening test. Levels exceeding ≥10 times the upper limit of normal (ULN) for the TTG-IgA assay, with confirmation of positive EmA IgA in a second blood sample while on a diet containing gluten can be used to diagnose CD.[80] Only antibody tests with calibrator curve-based calculation, and having the TTG-IgA ≥10 times ULN value within their measurement range, should be used. This approach has not been universally adopted as standard of care internationally and is inconsistent with other guidelines.[87]

In people with diabetes with positive TTG-IgA <10× ULN a small bowel biopsy with at least 4 biopsies from the distal duodenum and at least 1 from the bulb should be taken[80] to confirm the diagnosis of CD by demonstrating subtotal villus atrophy, as outlined in the Marsh classification.[88] Several biopsy samples should be taken, as CD can present with variable biopsy findings, and non-focal or "patchy" histopathologic lesions have been observed from duodenal samples in over 50% of children and up to 25% of adults.[89,90]

In the symptomatic child, a biopsy-sparing approach may be considered on a case-by-case basis in consultation with a pediatric gastroenterologist and the child and family. Initiation of a gluten-free diet (GFD) and resolution of symptoms serves as indirect evidence of the diagnosis.

In the asymptomatic child, evidence for a biopsy-sparing approach is limited in children with T1D and was not addressed by recent European guidelines.[80] The implications of a life-long commitment to be on a GFD in an individual with both CD and diabetes without symptoms is an important consideration and the decision to perform duodenal biopsies for confirmation of gastrointestinal pathology should be discussed with parents and the child.

There are challenges to broader implementation of assay cutoffs for diagnostic purposes that include a lack of international standardization, assay variability, as well as CD and diabetes related factors.[91,92] For example, TTG-IgA positivity at the time of screening may be transient and there are several reports of spontaneous normalization of CD antibodies[93,94] emphasizing serological follow-up (in 3–6 months) instead of immediate recourse to duodenal biopsy and the need for a duodenal biopsy to verify the diagnosis, especially in asymptomatic individuals with diabetes.[95]

Children with coexisting T1D and CD have been observed to have low HDL-cholesterol and increased LDL-cholesterol, significantly higher rates of concomitant autoimmune thyroid disease, and an increased risk for depression and disordered eating behaviors. These associations indicate that children and adolescents with both conditions should have regular assessments of their serum lipid profiles, annual screening of thyroid function, and regular screening for depression and eating disorders.[96–98]

A GFD normalizes the bowel mucosa, frequently leads to disappearance of antibodies, and has an impact on the normalization of lipid profile,[99,100] but may not necessarily impact glycemic management.[68,74,101] There is a report, that GFD is associated with greater glycemic excursions and inadequate nutritional intake in youth with T1D and CD; therefore, clinical management should also address glycemic variability and dietary quality and both people with diabetes and their diabetes care team should be vigilant as insulin requirements may change during transition to the GFD.[102,103] The aims of the GFD include reduction of the possible risk of gastrointestinal malignancy and the effects of subclinical malabsorption that may include osteoporosis, iron deficiency, and growth failure.[68,104,105] Long-standing CD in the context of T1D may be associated with an increased risk of retinopathy,[106] and the increase the risk of albuminuria is increased in those not maintaining a GFD.[107,108] There are also reports of increased risk for microvascular and potentially for macrovascular complications in T1D youth with comorbid CD.[108–110]

An important consideration for children and their families relates to the lifestyle impact because of transition to a GFD, especially in the context of diabetes. Children diagnosed with CD should receive education and support from an experienced pediatric dietitian knowledgeable about the GFD. Educational materials for youth with diabetes and families should be made available, that address both dietary issues and adaptation to a GFD in home, school and social settings.[111] Online education for GFD teaching is a helpful tool in teaching families with T1D and CD.[112]

Suboptimal maintenance of a GFD may be associated with reduced quality of life, worse glycemic management, and lower height SDS.[100,113] Diabetes-related factors such as HbA1c and symptoms are also important contributors to lower QOL in T1D youth with both conditions.[114]

The prevalence of CD is increased among first-degree relatives of children with T1D, and consequently family members of a child with newly diagnosed CD should also be screened.[95]

4.4 | Primary adrenal insufficiency (Addison's disease)

Up to 2% of people with T1D have detectable anti-adrenal autoantibodies.[42,115,116] The HLA DRB1*04-DQB1*0302 (primarily DRB1*0404) and DRB1*0301-DQB1*0201 haplotypes define subjects at high-risk for

adrenal autoimmunity,[117] while homozygosity for the MHC (HLA) class I chain-related gene A (MICA) polymorphism 5.1 defines those at highest risk for progression to overt Addison's disease.[118] A person with T1D who has the DRB*0404 allele and 21-hydroxylase antibodies has a 100-fold risk of developing Addison's disease. Adrenal insufficiency may be associated with T1D as part of the autoimmune polyglandular syndromes (APS-1 and APS-2).[119] The immunodeficiency, polyendocrinopathy and enteropathy, X-Linked syndrome (IPEX) is an extremely rare monogenic polyendocrine disorder that presents in the perinatal period or infancy with diabetes (with an overall prevalence of 60%) or chronic diarrhea due to autoimmune enteropathy. Other manifestations are eczematous dermatitis, autoimmune hypothyroidism, autoimmune cytopenias, and glomerulonephritis due to a mutation in the forkhead box P3 (FOXP3) gene, which encodes a transcription factor the development and function of regulatory T cells.[120,121]

Addison's disease is suspected by the clinical picture of frequent hypoglycemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatremia and hyperkalemia as well as severe or recurrent infections.[122] The diagnosis is confirmed by demonstrating a low serum cortisol response to an ACTH stimulation test and positive anti-adrenal (21-hydroxylase) antibodies. Treatment is urgent and lifelong, consisting of glucocorticoid and mineralocorticoid (fludrocortisone) replacement. In asymptomatic children with positive adrenal antibodies, a rising plasma ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency. Longer-term data have shown a 4-fold greater risk of mortality in youth with both diabetes and adrenal disease, as compared with diabetes alone.[123] These individuals with diabetes require additional vigilance to balance the challenges of diabetes care, optimize metabolic outcomes, and reduce risks of hypoglycemia and diabetic ketoacidosis, and appropriate management and prevention of adrenal crises.[124] It is important to prevent adrenal crises through education, emergency cards, and adjustment of glucocorticoid treatment (stress dose glucocorticoids) in case of intercurrent medical illness, trauma, surgery, or invasive procedures, as well as to identify and treat adrenal crises in a timely manner.[124]

4.5 | Autoimmune gastritis

Parietal cell antibodies (PCA) are the principal immunological markers of autoimmune gastritis and react against the H^+/K^+ ATPase of the gastric parietal cells.[116,125] Chronic damage to the proton pump may result in hypo- or achlorhydria, hypergastrinemia, and iron deficiency anemia due to decreased gastric secretion and decreased iron absorption.[126] PCA may also inhibit intrinsic factor secretion, leading to vitamin B12 deficiency and pernicious anemia.[127] T1D is associated with an increased risk of parietal cell antibody positivity,[128] with prevalence rates in children ranging from 5.3% to 7.5%.[129–131] Physicians should be aware of the possibility of PCA in children and adolescents with T1D in cases of unclear anemia (microcytic as well as macrocytic) or gastrointestinal symptoms, but routine screening is not recommended. In youth with diabetes with positive PCA, blood count, iron status, and vitamin B12 status should be assessed. If the individual with diabetes with positive PCA has gastrointestinal symptoms, a gastroscopy should be considered.

4.6 | T1D and systemic autoimmune diseases

In addition to organ-specific autoimmune diseases, other non-organ-specific, or systemic autoimmune diseases, such as JIA, Sjogren syndrome, psoriasis, and sarcoidosis may also develop in individuals with T1D.[132] In children with T1D, JIA is the most frequently encountered non-organ-specific autoimmune condition.[132] The disease affects girls twice as often as boys. There is growing evidence for the common genetic background of JIA and T1D, which is associated with a mutation in the PTPN22 gene encoding an enzyme inhibiting the T-cell activation pathway.[133] Sjögren's syndrome is a systemic autoimmune disease that mostly affects lacrimal and salivary glands. The spectrum of the disease ranges from dryness syndrome to systemic disease of exocrine glands. There are single case reports of T1D occurring in individuals with Sjögren's syndrome.[134]

4.7 | Combined autoimmune conditions: APS and APECED

The co-occurrence of vitiligo and other autoimmune conditions should raise the diagnostic consideration of APS, an immune endocrinopathy characterized by the coexistence of at least two endocrine gland insufficiencies. APS-1, also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare autosomal recessive disease that often presents in childhood and is characterized by the development of adrenal insufficiency, chronic mucocutaneous candidiasis, and hypoparathyroidism. It is caused by a mutation in the autoimmune regulator gene (AIRE) on chromosome 21q22.3.[135,136] The clinical diagnosis is defined by the presence of at least two components of the classic triad including chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and adrenal insufficiency. Other common features of the disease are hypergonadotropic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, T1D, and gastrointestinal dysfunction.[137] APS-2, which is much more common than APS-1 and usually commences later in life than APS-1, is defined by the combination of at least two of three diseases in the same individual: autoimmune adrenal insufficiency, T1D, and autoimmune thyroid disease. APS-2 may also be associated with IgA deficiency, Graves' disease, primary hypothyroidism, hypogonadism, hypopituitarism, Parkinson's disease, myasthenia gravis, CD, vitiligo, alopecia, pernicious anemia, and Stiff-man syndrome. APS-2 is usually associated with class II HLA alleles, particularly DRB1*0401 and DRB1*0404.[120] The prevalence of T1D is 4% to 20% in APS-1 and 60% in APS-2.[138,139] Approximately 3% to 8% of individuals with diabetes or autoimmune thyroid disease have CD.[140] The female-to-male predominance of youth with T1D and thyroid disease is much greater (6.4:1) than the ratio for youth with diabetes alone (1:1).

5 | T1D RELATED SKIN CONDITIONS

5.1 | Skin problems related to diabetes therapy and chronic devices use

5.1.1 | Insulin-induced lipodystrophy (lipohypertrophy and lipoatrophy)

Insulin-induced lipodystrophy remains an important complication in the care of diabetes. LH and LA are well-recognized dermatological complications of subcutaneous insulin administration.[141] It is important for physicians to be aware of and recognize these insulin-related skin complications.[142]

Lipohypertrophy

LH is a frequent complication of insulin therapy characterized by painless induration and swelling caused by fibrous and poorly vascularized lesions in the subcutaneous adipose tissue confined to frequently used insulin injection sites.[143] A recent study showed higher levels of proinflammatory cytokines and anti-insulin antibody are associated with lipodystrophy in T1D.[144] Etiologic factors include tissue trauma caused by substandard injection technique, insufficient injection site rotation, repeated injections into a small area, and reuse or excessive length of the needles. Insulin also has a direct anabolic effect on local skin leading to fat and protein synthesis that is a contributing factor in the pathogenesis of LH.[145] As lipohypertrophic areas are relatively painless, youth with diabetes often continue to use the same area rather than move to a new, more sensitive site. Initial skin changes can be subtle and manifest only as thickening of skin. This can be easily missed by visual inspection and palpation of the skin in areas used for injection is recommended to appreciate the soft, lipoma-like nodules.[146] There are important consequences of LH including suboptimal glucose management and glycemic variability that may increase the risk of diabetes complications.[147] In addition, LH is associated with increased insulin doses by up to 25% due to reduced insulin absorption and variable glycemic excursions related to alterations in the duration of insulin action.[148] In one study, people with diabetes with LH were found to have a 7-times higher risk of unpredictable unexplained hypoglycemia than those without LH.[142] LH can be prevented by adhering to proper insulin injection technique, including regular injection site rotation and limited insulin needle reuse.[149] Needles should be as short as possible to minimize tissue trauma and avoid inadvertent intramuscular administration, especially in thin individuals.[150] Four mm needles are associated with the least risk of causing tissue trauma and inadvertent intramuscular injection; however, choice of needle size must be individualized.[151] Ultrasound has been used to evaluate insulin-induced LH.[152] The method is more sensitive than palpation; ultrasound verified LH was detected in more than 80% of cases. In individuals with diabetes with significant, widespread LH, ultrasound can be used to find suitable sites for injections ("ultrasound injection map"). In practice, physical examination of injection sites for the presence of LH is a key component in the care of children with T1D. Individuals with diabetes should also be taught to examine their own injection sites and how to detect LH.[153]

Lipoatrophy

LA is a form of localized lipodystrophy characterized by localized loss of subcutaneous adipose tissue at the site of insulin injection. It appears to be the result of a lipolytic reaction to impurities or other components in some insulin preparations, as its prevalence has fallen to only 1% to 2% with the increasing use of purified insulin.[154,155]

The mechanism of LA is poorly understood; an immune pathogenesis seems likely, and it is seen more often in individuals with diabetes who have other evidence of autoimmunity.[156] Other theories of causation include cryotrauma from refrigerated insulin, mechanical trauma due to the angle of injection, surface alcohol contamination, or local hyperproduction of tumor necrosis factor alpha from macrophages induced by injected insulin.[157] Repeated use of the same insulin injection site and multiple usage of the same pen needle increases the risk of LA.[158]

Treatment options are limited and include changing the site of injection or infusion cannula and switching insulin analogues[159]; however, this does not always lead to complete resolution of lesions.[160,161] Treatment with steroids, given orally (daily low dose prednisolone)[160] or injection of dexamethasone[161] and cromolyn sodium[155] into the lipoatrophic lesions has been reported to be successful in anecdotal cases.[162,163]

5.1.2 | Dermatological manifestations of diabetes technology devices: Continuous subcutaneous insulin infusion and continuous glucose monitoring

CSII and CGM devices are widely used in youth with T1D as standard therapy or as part of a closed-loop-system as they may improve glycemic management and enhance treatment flexibility.[164] With increasing popularity, a wide range of reported skin reactions and dermatological complications to CSII and CGM devices are frequently reported. Additional CGM and CSII specific skin concerns are described in ISPAD 2022 Consensus Guidelines Chapter 16 Diabetes Technologies: Glucose monitoring and Chapter 17 on Diabetes Technologies: Insulin delivery.

The frequency of reported skin reactions among pediatric CGM users has significant individual variation and skin issues have been reported to be as high as 39%,[165–167] which may affect management and be a barrier to consistent long-term use. A recent systematic review of cutaneous complications in CGM users from clinical trial data reported erythema (55%), pruritus (11%), and induration (9%).[168] Among those using insulin pumps, localized eczematous reactions at the site of infusion set insertion were noted in 14% of youth in one study[169] and a survey of 143 youth documented that nearly half of the cohort reported non-specific eczema.[170]

A history of atopy and the type of adhesive used in a device plays a key role in development of allergic contact dermatitis. Acrylate monomers, that include ethyl cyanoacrylates as well as isobornyl acrylate (IBOA), are common components in the preparation of adhesives, which are known to be a potent source of contact dermatitis.[171,172] In addition, contact dermatitis can occur on the manufacturer adhesives to colophonium and N, N-dimethylacrylamide.[172–174] Acquired

leukoderma (localized areas of depigmentation), have been described with direct skin contact and has been linked to the depigmenting substance hydroquinone monomethyl ether (HMME).[175] There is a need for manufacturing changes to improve breathability and reduce trapped moisture that contribute to skin reactions with the current technologies.[176] Initiatives for full and accurate labelling of the chemical composition of devices were recently presented.[177]

Scarring is another potential dermatological complication from CGM and CSII and appears to be more common in CSII. Scarring manifests as small hypo- or hyperpigmented lesions of fibrous tissue. Although it is unclear whether scarring affects sensor accuracy or insulin absorption, it may disrupt the insertion process of sensors or cannulas, and scarred areas should therefore be avoided.[157,178]

CSII can lead to lipodystrophy, whereas LA is less common than LH.[158,161] CGM use is not thought to contribute to lipodystrophy and a study indicated that CGM accuracy is not compromised in LH.[179]

The prevention of these skin-related complications includes good nutrition, hydration, site rotation, correct device placement, proper removal technique, and prophylactic skin care for optimal skin integrity.[180] Skin preparation should include exfoliation, trimming hair, and removing oil before adhesive placement to maximize adhesion and minimize irritation. Key steps include appropriately cleaning the skin and drying it completely before attempting to place CGM sensors and CSII catheters, and use adhesive barriers, tackifying agents or possibly off-label steroid sprays (e.g., fluticasone) prior to insertion for those with known prior reactions.[181] Sweating could be mitigated by applying antiperspirant to the skin before insertion.[182] Removal of adhesives by including use of removal agents may also be used to minimize tissue damage. Moreover, individuals with diabetes should be taught to monitor sites for pain, edema, erythema, warmth, or suppuration.

5.1.3 | Insulin edema

Insulin edema is a complication of insulin therapy that may occur shortly after the initiation of intensive insulin therapy in newly diagnosed with suboptimal glycemic management[183] or following high dose insulin therapy in poorly nourished individuals with diabetes.[184,185] The true incidence of insulin edema is not known and insulin edema is reported most often among children and adolescents.[184] Despite its self-limiting nature, it is rarely observed with pleural effusion, heart failure, or generalized edema.[186] The mechanisms resulting in insulin edema is the deficiency of insulin, which results in a catabolic state.[187,188] Intensive fluid resuscitation during the initial phase of treatment may lead to extravasation of fluid into the subcutaneous tissue, exacerbating edema.[189]

Moreover, the severity of edema negatively correlates with BMI, with the most severe cases occurring in the severely underweight individuals with diabetes, further suggesting a link between the resolution of the catabolic state upon the commencement of insulin and the development of edema.[189]

Insulin edema often improves spontaneously in 1 to 3 weeks and decreased insulin doses can also help to reduce edema.[184] Short-term diuretic treatment,[185] salt restriction, and ephedrine[190] have been described and may be effective in the treatment of acute edema, but are rarely indicated. The resumption of insulin necessary for the management of T1D should be gradual and accompanied by a frequent reassessment of fluid status.[191,192]

5.2 | Dermatological conditions associated with diabetes

5.2.1 | Necrobiosis lipoidica diabeticorum

Necrobiosis lipoidica is an uncommon chronic granulomatous dermatitis characterized by plaques on the shins of tibia with red-brown edges and atrophic, yellow-brown, telangiectatic centers.[193,194] The prevalence of NL ranges from 0.3% to 1.2% among youth with diabetes mellitus,[195] of which two-thirds have T1D. NL is generally asymptomatic unless it is ulcerated and painful in 25% to 33% of cases.[196] NL is more common in females than in males.[197]

NL usually appears during young and middle adulthood,[198] although there are a few studies reporting cases in childhood and adolescents.[199,200] The pretibial region is the area typically affected and only lesions rarely occur on hands, fingers, face, forearms, and scalp[197] and, recently reported, also on the trunk.[201] It has been suggested that NL is possibly a manifestation of microangiopathy, but the impact of suboptimal glucose management as a causative factor in the development and progression of NL lesion remains controversial and there are limited data available in the pediatric population.[202]

The treatment of NL is challenging; initial therapy includes topical, intralesional or systemic corticosteroids, but responses vary. Approximately 17% of cases spontaneously remit after 8 to 12 years.[203] Some authors have reported a beneficial effect from smoking cessation and improved blood glucose management.[204] In case reports, doxycycline,[205] anti-TNFα agents,[206] JAK1/2 inhibitor[207] showed promising results in the management of this condition.

5.2.2 | Vitiligo

Vitiligo vulgaris, or skin depigmentation, occurs more commonly in T1D; 1% to 7% of all individuals with diabetes have vitiligo compared to 0.2% to 1% of the general population.[208] The significant correlation between vitiligo and T1D might result from a similar pathogenesis of autoreactive cytotoxic T-cell mediated destruction in both diseases.[209] The destruction of melanocytes may be mediated by cytotoxic CD8 T-cells. Measurement of 25-hydroxyvitamin-D levels and supplementation should be considered, since vitamin D deficiency is common in people with vitiligo.[210] Treatment of vitiligo is often unsatisfactory. Individuals with diabetes should be advised to avoid the sun and to use broad-spectrum sunscreens. For localized vitiligo, topical corticosteroids or calcineurin inhibitor-based creams are preferred, whereas Ultraviolet-B-light-treatment may be effective for generalized vitiligo.[211]

5.2.3 | Other diabetes-related skin conditions

Other diabetes-associated skin conditions include granuloma annulare, diabetic dermopathy, acquired perforating dermatosis, and bullosis diabeticorum, or diabetic bullae. There are also other skin disorders that occur more frequently in individuals with diabetes, such as pruritus, xerosis, lichen planus, finger pebbles, and skin tags.[146,212] Hyperglycemia leads to important metabolic and immunological alterations, so that people with diabetes tend to be more susceptible to skin infections.[212]

5.2.4 | Limited joint mobility in childhood diabetes

The cause of limited joint mobility (LJM) is the deposition of abnormal collagen in the connective tissues around the joints. The condition is also known as diabetic cheiroarthropathy and is linked to long-standing diabetes mellitus and suboptimal diabetes management. The prevalence is 8% to 58% in individuals with diabetes[213] and increases with age.[214,215] The risk of developing LMJ is related to higher HbA1c levels.[214] LJM changes begin in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the little finger and extend radially; and in some, the distal interphalangeal (IP) joints are involved. The limitation is painless and non-disabling in most instances. Individuals with diabetes may present with an inability to firmly press the palmar surfaces of each of their hands together ("prayer sign") or against the surface of a table when their forearms are perpendicular to the surface of the table ("tabletop sign").[216] These changes occur as a result of periarticular expansion of connective tissue. In a recent study, ankle joint mobility (AJM) was evaluated using an inclinometer and found to be significantly reduced in youth with T1D, and both plantar and dorsiflexion was significantly lower in subjects with diabetes than in controls.[217] LJM is strongly associated with microvascular[218] and macrovascular changes and diagnosis of LJM should prompt a workup for related sequelae.[219] There is no curative treatment. Symptomatic people with diabetes may benefit from non-steroidal anti-inflammatory drugs or targeted injection of corticosteroids.[220] LJM is best managed with improved glycemic management as well as regular stretching to maintain and minimize further limitations in joint mobility.[221] Medical treatments targeting the formation of glycosylated end products accumulating on collagen and other connective tissues that are said to be responsible for the development of LJM, have so far proved to be unsuccessful.[213]

6 | BONE HEALTH AND TYPE 1 DIABETES

Accumulating evidence suggests that bone mineral density (BMD), bone structure, fracture risk and bone turnover markers (BTM), and bone metabolism are altered in T1D. Published results are, however, conflicting due to heterogeneity of the study populations in relation to age groups, metabolic outcomes, and method of BMD assessment. It has repeatedly been demonstrated that T1D is associated with an increased risk of fracture.[222,223]

A population-based cohort reported that risk of incident fracture in individuals with diabetes was higher across the lifespan and impacted both sexes equally. In childhood (0–19 years), the increased risk for all fracture types was higher by 14% (range 1%–29%) and the rate was double in T1D adults as compared to healthy controls.[222] The risk for the increased fracture rate seems to be associated to lower BMD; however, other factors could also be at play.[224–228]

Despite the higher risk of fracture, abnormal bone density as assessed by dual X-ray absorptiometry (DXA) is not always consistently low in youth and adults with T1D, with potential biases including pubertal status, diabetes duration, and differing methods to assess BMD.[224,229–232] However, decreased trabecular BMD has been demonstrated by peripheral Quantitative CT (pQCT) measurements, assessing volumetric bone changes[233,234] and in pubertal T1D girls with normal BMD altered skeletal microstructure has been reported.[235] Data suggest microvascular disease mediates microarchitectural changes by increasing cortical porosity and is associated with lower bone turnover. There is no direct evidence linking microangiopathy to fracture incidence.[236] Finally, a bone health index[237] and bone geometry has been demonstrated to be altered in T1D children and associated to bone turn over markers.[238]

Furthermore, abnormal bone accrual (density and quality) in T1D[239] likely has a multifactorial etiology, involving reduced bone formation and abnormal bone quality.

The effect of increased HbA1c levels has consistently been demonstrated to be associated with low BMD[229,230,232,240] verified by a meta-analysis in 2021[241]; however, this observation was not confirmed in another recent meta-analysis.[242] As has been described in detail above, comorbidities such as CD and thyroid dysfunction can also negatively affect bone health in T1D,[228] but the true extent of their impact in children and adolescents is unclear.[243]

The influence of glucose metabolism on the regulation of bone metabolism seems to be complex and not yet fully known. Bone turnover markers (BTM) seem to be affected in T1D youth.[244] Altered BTM have been shown as early as within the honeymoon period of T1D in children and adolescents[245] with associations described between bone resorption and increased insulin sensitivity.[246] With longer T1D duration BTM also seems to be affected,[247] demonstrating increased bone resorption by increased levels of RANKL and lower OPG levels in 71 T1D individuals aged 5–18 years compared to 50 controls; however, OPG / RANKL data are conflicting in the literature. Another pediatric study demonstrated higher levels of CTX z-scores (another bone resorption marker) in 173 T1D children and adolescents aged 7–18 years of age of to be associated to lower levels of HbA1c, also suggesting an interaction between bone and glucose metabolism.[248]

Regular assessment of bone health using bone densitometry is still controversial and not recommended. In specific populations, such as CD, evaluation of bone health should be considered, as the mechanisms involved in abnormal BMD in CD in association with T1D may not only be due to impaired absorption of calcium or vitamin D, but also include inflammatory pathways. In all youth with T1D, adequate nutrition including calcium, maintenance of normal vitamin D levels,

TABLE 1 Summary of common complications and associated conditions in children and adolescents with type 1 diabetes

Comorbid autoimmune disease	Symptoms	Risk factors	Screening and confirmatory tests	Screening recommendations
Hashimoto's thyroiditis	Decreased linear growth Painless goiter Fatigue Cold intolerance Bradycardia Weight gain Hypoglycemia may occur	Age Duration of T1D Presence of GAD autoantibodies CD	Antithyroid peroxidase antibodies, antithyroglobulin antibodies, TSH, T4 or free T4	At diagnosis (after glucose management is established): anti-thyroid peroxidase and anti-thyroglobulin antibodies, TSH Every 2 years: TSH (sooner if positive thyroid antibodies at diagnosis or with symptoms)
Graves' disease	Weight loss Normal/increased appetite Palpitations Heat intolerance Goiter Proptosis Suboptimal glycemic management	Age Duration of T1D Presence of GAD autoantibodies	Thyroid stimulating immunoglobulin, TSH, T4 or free T4, T3	Symptom related
Celiac disease	Most often asymptomatic Hypoglycemia Impaired linear growth Diarrhea Nausea, vomiting, abdominal pain	Affected first degree relative Other autoimmune disease	Tissue transglutaminase antibody Anti-endomysial antibody	Initial year of diagnosis 2–5 years intervals (sooner if symptomatic or First degree relative with CD)
Autoimmune gastric disease	Most often asymptomatic Anemia (pernicious anemia or iron deficiency anemia)	Thyroid autoimmunity Persistence of GAD autoantibody titers	Parietal cell autoantibodies (PCA) Blood count, vitamin B12, ferritin, gastrin	Symptom related
Primary adrenal insufficiency (Addison's disease)	Hypoglycemia Fatigue Nausea Weight loss Salt craving Postural hypotension Hyperpigmented skin and mucosa	First degree relative with disease	21-hydroxylase antibodies, Plasma ACTH, 8 AM serum cortisol, electrolytes, plasma renin activity	Symptom related
Vitiligo	Sharply delineated skin depigmentation, affecting extremities, face, and neck and trunk	Thyroid disorder autoimmune polyglandular syndrome (APS) and vitamin D deficiency	Clinical diagnosis	Symptom related
Alopecia	Non-scarring, round and/or oval patches of hair loss.	Polyglandular autoimmune syndrome type 2	Clinical diagnosis	Symptom related
Juvenile idiopathic arthritis	Joint(s) inflammation characterized by swelling, limitation in the range of motion, tenderness; symptoms must be present for at least 6 weeks		Clinical diagnosis	Symptom related
Sjogren syndrome	Xerophthalmia (dry eyes) and xerostomia (dry mouth); recurrent parotitis, with other organ involvement		Clinical diagnosis	Symptom related
Psoriasis	Skin disorder with thick, red, bumpy patches covered with silvery scales		Clinical diagnosis	Symptom related
Sarcoidosis	Non-caseating granulomas, predominantly in the lymph nodes, lungs, eyes, and skin.		Clinical diagnosis	Symptom related
Sclerodema diabeticorum	Thickening of the skin with characteristic "peau d'orange" appearance		Clinical diagnosis	Symptom related

Abbreviations: ACTH, adrenocorticotropic horm; CD, celiac disease; GAD, glutamic acid decarboxylase antibodies; T1D, type 1 diabetes mellitus; T4, thyroxine; TSH, thyroid stimulating hormone.

and avoidance of smoking and regular weight-bearing exercise is important for bone health; however, more intervention studies are needed.[249] Screening for vitamin D deficiency, particularly in high-risk groups (CD, autoimmune thyroid disease, darker skin tone), should be considered in young people with T1D.

7 | ORAL HEALTH

Young people with T1D are at increased risk of oral health problems, including periodontal disease, gingivitis, oral infections, and caries, with a greater risk in those with higher HbA1c.[250–253] High blood glucose levels contribute to reduced salivary flow, which contributes to tooth decay and periodontal bone loss. Furthermore, there is evidence that elevated levels of pro-inflammatory mediators in sub-optimally managed diabetes and oxidative stress within the gingival tissues of people with diabetes play a role in the observed increased periodontal destruction.[254] Treatments for hypoglycemia such as sweetened carbonated beverages and candies may also increase the risk of tooth decay. In adults with T1D, suboptimal glycemic management is associated with an increased risk of future tooth loss.[255] Despite the increased risk, there is some evidence that children with diabetes have substandard oral hygiene practices.[251] Therefore, as part of preventive care, maintenance of oral health and regular dental review are recommended in young people with T1D.

AUTHOR CONTRIBUTIONS

All authors engaged in multiple meetings and discussions and reviewed the relevant content and contributed to the writing and editing of this guideline.

CONFLICT OF INTEREST

The authors have declared no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The relevant studies that support the recommendations are available in the references.

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How to cite this article: Fröhlich-Reiterer E, Elbarbary NS, Simmons K, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Other complications and associated conditions in children and adolescents with type 1 diabetes. *Pediatr Diabetes*. 2022;23(8):1451-1467. doi:10.1111/pedi.13445

DOI: 10.1111/pedi.13446

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

ISPAD clinical practice consensus guidelines 2022: Management of children and adolescents with diabetes requiring surgery

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KEYWORDS: anesthesia, bariatric, children, continuous glucose monitoring, fasting, insulin pump therapy, surgery, type 1 diabetes, type 2 diabetes

1 | WHAT IS NEW OR DIFFERENT

- Management of youth with different types of diabetes undergoing surgery
- Use of diabetes technologies (pumps and sensors) in youth undergoing surgery
- Management of youth with type 2 diabetes (T2D) treated with new oral medications
- Management of diabetes in youth undergoing bariatric surgery

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

Glycemic goals for surgery are to

- Maintain blood glucose level (BGL) in a range of 5–10 mmol/L (90–180 mg/dl). **C**
- Prevent hypoglycemia. **E**
- Prevent the development of diabetic ketoacidosis (DKA). **E**

Assessment of youth prior to surgery and/or anesthesia

- We recommend that young people with diabetes have a diabetes consultation prior to all types of surgery or anesthesia. **E**
- We recommend that young people with diabetes be formally reviewed by their diabetes team several days before elective surgery or a procedure under anesthesia for a thorough assessment of glycemia, ketones (urine/blood), and to create a formal plan for diabetes management prior to, during and after surgery and/or anesthesia. **E**
- If glycemia is suboptimal and surgery cannot be delayed, consider admission to hospital before surgery for acute optimization of glycemia. **C**

Preoperative care for youth with T1D, T2D or other types of diabetes requiring insulin

- Consider admission to hospital or day clinic with an anesthesiology team that has protocols for the management of diabetes, if receiving general anesthesia. **E**

- If outpatient surgery is planned, aim for glycemia to be in the target range and preoperative communication with the youth with diabetes and their families is essential. **E**
- The anesthesiologist is expected to be experienced in the management of insulin therapy in youth with diabetes and to have contact with the diabetes team in advance. **E**
- It is recommended that surgery is preferably scheduled as the first case of the day or on the surgical list, especially if performed in a day care setting. **E**
- An intravenous (iv) site for use pre- or intra-operatively to treat hypoglycemia is required. **E**
- The insulin regimen may need specific adjustments based on the procedure (major or minor surgery) and the pre-existing glycemia status. **E**
- If treated with an oral anti-hyperglycemic medication, this may also need to be modified. **E**
- Insulin is required, even if fasting, to avoid DKA. **A**
- BGL testing is required at least hourly to detect and prevent hypo- and hyperglycemia. **E**
- Measurement of urine or blood ketone level is advised if hyperglycemia >14 mmoL/L (250 mg/dl) is present. **E**
- Continuous subcutaneous insulin infusion (CSII) therapy can be continued in certain cases of minor elective surgery. **E**

Intraoperative care

- Monitor BGLs at least hourly during and in the immediate postoperative recovery phase. **E**
- Continuous glucose monitoring (CGM) can be used intraoperatively if deemed appropriate by the anesthesia provider and point-of-care (POC) BGL is validated concurrently. **E**
- Limited data exist on interactions between anesthetic agents and CGM, thus concurrent POC BGL monitoring is required. **E**
- Consider using iv infusion with dextrose (5% dextrose/0.9% sodium chloride) together with iv insulin infusion during any major surgery, and for young people treated with NPH insulin **E**.
- Consider an iv infusion of 0.9% sodium chloride, initially without dextrose, during minor surgery or procedures lasting less than 2 h if the young person with diabetes is treated with a multiple daily injection (MDI) regimen or CSII. **C**
- Adjust dextrose infusion and subcutaneous insulin to maintain BGL in the range 5–10 mmol/L (90–180 mg/dl). **C**
- If there is an unexpected acute hypotensive episode, 0.9% sodium chloride must be infused rapidly, however avoid potassium-containing fluids. **E**

Postoperative care

- Once the young person can tolerate oral nutrition, resume their usual insulin regimen. **E**
- Give short- or rapid-acting insulin (based on the usual insulin: carbohydrate ratio and correction factor). **E**
- It may be appropriate to give the first postoperative dose of insulin after initial oral intake to be sure that food is tolerated. **E**
- Insulin requirements may vary after surgery due to change in oral intake, nausea, stress, pain, and inactivity; therefore, frequent CGM/BGL measurements are recommended for 24–48 h following surgery. **E**
- Some CGM systems can provide false readings when exposed to specific medications (including acetaminophen), thus concurrent POC BGL monitoring may also be indicated. **C**
- BGL target of 7.8–10 mmol/L (140–180 mg/dl) in the postsurgery intensive care unit (ICU) setting is suggested. **C**

Special situations

Acute or emergency surgery

- DKA can mimic an acute abdomen. If DKA is present (pH < 7.3 and/or bicarbonate <18 mmol/L, and ketosis), follow an established treatment protocol for DKA and, if possible, delay surgery until acidosis, ketosis, circulating volume and electrolyte deficits are stable or sufficiently corrected. **E**
- If not in DKA, start iv fluids and insulin management as for elective surgery. **E**
- During emergency major surgery in an acutely ill child, discontinue CSII therapy. **E**

T2D or other types of diabetes requiring oral medications alone

- Discontinue metformin on the day of surgery. **C**
- Discontinue sulfonylureas, thiazolidinedione, DPP-iv inhibitors, and GLP-1 analogs on the day of surgery. **E**
- For young people with diabetes undergoing a major surgical procedure, expected to last at least 2 h, monitor hourly BGLs and adjust dextrose infusion or iv insulin to maintain BGL in the range 5–10 mmol/L (90–180 mg/dl). **E**
- Restart medications once oral intake is tolerated, except metformin, which should be withheld for 24 h after a major surgery, and until normal renal function has been confirmed. Metformin can be restarted once oral intake is tolerated after minor surgery. **E**

General recommendations and considerations

- Whenever possible, plan surgery to be performed in centers with appropriate personnel and facilities to provide optimal care for young people with diabetes. **E**
- To ensure the highest level of safety, careful liaison is required between surgical, anesthesiology and diabetes care teams before admission to hospital for elective surgery and as soon as possible after admission for emergency surgery. **E**
- It is recommended that centers performing surgical procedures on young people with diabetes have perioperative management protocols. **E**
- Individual hospitals need to formalize guidance on the management of people with diabetes receiving CSII therapy, to allow

individuals the choice to continue their CSII during surgery when appropriate. **E**

- Use of CGM systems is recommended to trend glucose levels perioperatively, but routinely verify CGM data by POC BGL measurements. **E**

Minor surgery/procedures

- Young people undergoing minor surgery/procedures can be managed with basal insulin (glargine or reduced NPH insulin) and may not need iv insulin infusion. **E**
- Intravenous access must be placed. **E**
- May be suitable to continue with CSII providing basal insulin or with a temporary basal rate reduction. **E**
- Can leave CSII attached to the individual with diabetes as long as it is not in the surgical field or diathermy plane (especially with metal cannula). **E**

Major surgery

- An iv infusion with dextrose is required to keep glucose in the range 5–10 mmoL/L (90–180 mg/dl) during major surgery. **E**
- Monitor hourly BGL monitoring before, during, and after the procedure. **E**
- Coordination of the timing of preoperative food and fluid restrictions with the anesthesiologist is needed. **E**
- Require specific adjustment of the insulin schedule. **E**
- Require iv insulin infusion. **E**

3 | INTRODUCTION

The management of diabetes in young people now includes a wide array of insulin analogs, insulin delivery devices, and CGM. Safe management of young people with diabetes in the perioperative period requires not only an understanding of the pathophysiology of the condition requiring surgery but also a thoughtful consideration of the young person's specific diabetes treatment regimen, glycemia status, anticipated postoperative course, and the environment where they will be discharged. Therefore, it is essential that the surgeon and anesthetist (in particular) liaise with the diabetes team prior to and after any planned and especially any acute major surgery.

The current revised guidelines are based on the 2018 ISPAD Consensus Guidelines.[1] They are also informed by The National Evidence-Based Clinical Care Guidelines for T1D for Children, Adolescents and Adults from the Australasian Pediatric Endocrine Group and Australian Diabetes Society,[2] the Canadian Diabetes Association: Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada,[3] and the Association of Children's Diabetes Clinicians Care of Children under 18 years with Diabetes Mellitus Undergoing Surgery.[4] They also include recommendations from a comprehensive review of perioperative management for children with diabetes published in the anesthesiology literature.[5] Because there are few high-quality scientific papers on the management of young people with diabetes during surgery, the recommendations in this guideline are mostly based on expert opinion, in accordance with available evidence from pediatric studies and relevant adult literature. Where appropriate, guidelines for perioperative management of adults with diabetes used to inform these recommendations.

4 | PERIOPERATIVE GLYCEMIC GOALS

The stress associated with surgery leads to a complex neuroendocrine response characterized by hyperglycemia and a catabolic state, which may affect glucose homeostasis in people with and without diabetes. In adults undergoing cardiac surgery, repeated postoperative episodes of hyperglycemia, when compared with a single episode of hyperglycemia or normoglycemia, were associated with increased rates of infectious complications (12.1% vs. 8.2%), stroke (4.9% vs. 1.5%), and mortality (6.1% vs. 2.1%), despite use of a tight BGL management protocol.[6]

While there is limited evidence on the impact of preoperative suboptimal versus optimal glycemic management on surgical outcomes in young people with diabetes, studies in adults suggest that there is an increased risk of hyperglycemia-related postoperative complications.[7] Adults with T2D had an approximately 10-fold increased risk of postoperative wound infections[8] and, in this population, preoperative hyperglycemia was an independent predictor of infectious complications and length of hospital stay.[9] One recent study on postoperative outcomes in children with diabetes undergoing orthopedic surgery[10] reported that the 30-day complication, reoperation, and readmission rates for non-insulin treated children with diabetes were higher than for those without diabetes.

Based on the results of adult studies, to improve elective (non-urgent) major surgery outcomes, admission to hospital prior to elective surgery for the assessment and stabilization of people who do not achieve optimal glycemic targets should be considered, as well as adjustment of insulin doses prior to major surgery and for several days postoperatively.[11]

With regards to optimal perioperative glycemic targets, there are currently sufficient data in adults without diabetes, but few randomized clinical trials (RCT) in the pediatric population to give strong recommendations. Thus, this topic remains controversial. A study among critically ill adults showed benefits of intensive insulin therapy and tight glycemic management, based on a single center experience.[12] However, subsequent data are not consistent, and even suggest harm associated with tight glycemia in adult populations.[13] Furthermore, a large multi-center randomized international trial showed that a glycemic target of 8–10 mmol/L compared with a lower target of 4.4–7 mmol/L was associated with decreased 90-day mortality.[14] A Cochrane database systematic review found insufficient evidence to support strict glycemic management versus conventional management for the prevention of surgical site infections.[15]

5 | IS 5–10 mmol/L (90–180 mg/dl) AN APPROPRIATE BGL TARGET IN YOUNG PEOPLE WITH DIABETES UNDERGOING SURGERY?

Some studies in adults with diabetes suggest that perioperative hyperglycemia is an independent risk factor for postoperative mortality and morbidity[16,17] Maintaining BGLs after surgery at <11.1 mmol/L (200 mg/dl) significantly reduced the incidence of deep wound infections in adults with diabetes undergoing coronary artery bypass.[18,19] However, tighter glucose management may carry a greater risk of both absolute and relative hypoglycemia in these individuals.[20] Such hypoglycemia may be particularly dangerous as people with diabetes may experience both unawareness and autonomic instability.[21,22] A Cochrane database review did not demonstrate significant differences for most outcomes when comparing intensive perioperative with conventional glycemic management. However, intensive glycemic management was associated with an increased number of hypoglycemic episodes.[19] Therefore, protocols with intensive glycemic targets (near-normal BGL) for individuals with diabetes undergoing surgical procedures are currently not supported.

Pediatric reports in individuals without diabetes include older retrospective studies, which have consistently shown an association between both hyperglycemia and hypoglycemia and poor outcomes in the pediatric critical care setting.[23–26] More recent RCTs with more specific glucose ranges among critically ill children, including post cardiac surgery (tight glycemia was 4.4 to 6.1 mmol/L; 80–110 mg/dl) and post burns, showed that children do not benefit from tight versus more liberal glycemic targets.[27–32] Systematic reviews and meta-analysis have shown that, while acquired infection was reduced, there was no decrease in 30-day mortality and a higher incidence of hypoglycemia was observed.[29,33] A multicenter RCT using CGM in pediatric critically-ill individuals was stopped prior to enrolment completion due to lack of benefit and evidence of harm in the low target arm (4.4–6.1 mmol/L; 80–110 mg/dl, median 109 mg/dl) compared with the higher target arm (8–10 mmol/L; 150–180 mg/dl). No significant differences were observed in mortality, severity of organ dysfunction, or the number of ventilator-free days, while participants in the lower-target group had higher rates of health care–associated infections and higher rates of severe hypoglycemia.[34]

The American Diabetes Association (ADA) published their guidelines for care in hospitalized adults with diabetes. The ADA recommends target BGL of 7.8–10 mmol/L (140–180 mg/dl) for most critical and non-critical ill people with diabetes. More stringent targets, such as 110–140 mg/dl (6.1–7.8 mmol/L), may be appropriate for selected individuals with diabetes if hypoglycemia can be avoided.[35] Glycemic targets for individuals with diabetes in the perioperative period should be 80–180 mg/dl (4.4–10.0 mmol/L).[35] Once iv insulin therapy has been initiated, BGL should be maintained between 8 and 10 mmol/L (140 and 180 mg/dl).

Our recommendation for glucose target in the pediatric diabetes population is quite similar. Although appropriate perioperative glycemic targets for minor surgical procedures are less clear, studies in adults that compared different methods of achieving glycemic management during minor and moderate surgery did not demonstrate any adverse effects of maintaining perioperative glycemic levels between 5 and 11 mmol/L (~90–200 mg/dl). Therefore, based on the available data, it seems reasonable to aim for BGL in the range 5–10 mmol/L (90–180 mg/dl) during all surgical procedures in children with diabetes, followed by a treatment target of 7.8–10 mmol/L (140–180 mg/dl) in the postsurgery ICU.

6 | IS THERE A ROLE FOR SUBCUTANEOUS GLUCOSE MONITORING DURING THE PERIOPERATIVE PERIOD?

The most frequently used methods for perioperative glucose monitoring are still repeated venous, arterial, or capillary BGLs, which may minimize intermeasurement variability. Individuals may be particularly prone to glucose variability and hypoglycemia in the perioperative setting, given fasting requirements, variation in insulin administration, and physiologic derangements, including surgical stress.

CGM provides a potential option of intensively monitoring glucose levels before, during, and after surgery, where there are benefits to maintaining euglycemia. However, evidence for the accuracy, readability, and effect on glycemia and prognosis using CGM in the operative setting is still limited. The overall accuracy and reliability of CGM systems during and postsurgery may be variable (correlation coefficient between CGM and conventional glucose monitoring methods ranges from 0.69 to 0.92). A small study in children without diabetes undergoing cardiac surgery showed a high measurement failure rate in the operating theater, which was thought to be due to interference with electrical equipment, though not affected by hypoglycemia, inotrope use or edema.[36] A more recent study in 12 adults, comparing Dexcom G6 factory-calibrated CGM with BGL obtained during elective abdominal surgery, reported encouraging results, with a mean absolute relative difference (MARD) of 12.7 ± 8.7%, 99.2% of CGM measurements within Clarke error grid zones A and B, and CGM overestimated reference glucose by 1.1 ± 0.8 mmol/L.[37]

Another option is the use of intermittently scanned CGM (isCGM) (FreeStyle Libre system).[38] Intermittent glucose monitoring using the FreeStyle Libre system was assessed among 8 critically ill adults with diabetes and showed high test–retest reliability and acceptable accuracy when compared with arterial BGL measurement.[39] However Freestyle Libre should not be used during Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or high frequency electrical heat (diathermy) treatment as stated by the manufacturer. This applies also to Dexcom CGM.

Some drugs can interfere with CGM results. In particular, high doses of acetaminophen (paracetamol) are known to cause false elevations of glucose values (maximum up to 61 mg/dl difference) for up to 8 h.[40] Possible interference has been reported for hydroxyurea with Dexcom G6 and drugs like lisinopril, albuterol and atenolol with Medtronic Guardian and Dexcom G4 systems.[41,42] Further studies are

needed to investigate CGM accuracy with commonly used anesthetic agents.

Users of CGM in the perioperative setting should be aware of the possible time lag between sensor readings and BGL especially in situations of rapidly changing BGLs. An effect of compression on the sensor known as "compression artifact" should be also taken into account and the position of the sensor on the operating table should be free of possible compression and, as far away as possible from the operative field.

Looking to the future, the availability of CGM glucose measurement at least every 5 min and the additional information provided by CGM glucose trends have the potential to improve perioperative glycemic management for children and adolescents with diabetes.

7 | CLASSIFICATION OF PROCEDURES AND PRESURGICAL ASSESSMENT

For the management of young people with diabetes undergoing surgery, it is helpful to divide procedures into two main categories: major and minor surgery. It is important to note that sometimes management of "major" surgery in a child with stable diabetes may be less complex than a "minor" surgery in a child with suboptimal glycemia and/or limited social support.

(a) *Minor Surgery* refers to short procedures, (usually less than 2 h), with/without sedation or anesthesia, where rapid recovery is anticipated, and the child is expected to be able to eat by the next mealtime (within 2–4 h). Examples include day clinic and ambulatory procedures like endoscopies, imaging studies, adeno-tonsillectomy, grommet insertion, or simple procedures for hospitalized individuals such as dressing changes or cancer treatments.

(b) *Major Surgery* includes any surgery or investigation under anesthesia that is more than minor, typically >2 h, have a high likelihood of postoperative nausea, vomiting or inability to adequately feed postoperatively.

Prior to elective surgery, young people with diabetes should have a thorough assessment of glucose profile, and when appropriate ketone measurement (urine/blood), and a formal plan for diabetes management formulated for surgery and/or anesthesia. If major surgery is planned, electrolyte status should also be assessed.

If glycemia is known to be sub-optimal and surgery cannot be delayed, admission to hospital before surgery for acute stabilization of glycemia should be considered.

8 | PREOPERATIVE CARE FOR YOUNG PEOPLE WITH DIABETES TREATED WITH INSULIN

- Whenever possible, surgery should be scheduled as the first case in the morning so that prolonged fasting is avoided and diabetes treatment regimens can be most easily adjusted.
- Based on the hospital regulations, young people with diabetes can attend the hospital or day clinic on the same day or be admitted before surgery if receiving general anesthesia. If outpatient surgery is planned, glycemic status should be in target. If the person with diabetes has other reasons to be in hospital or diabetes is not well controlled, then admission before surgery is recommended.
- The anesthesiologist should be experienced in the treatment of insulin dependent diabetes and have contact to the diabetes team in advance.
- Specific adjustment of insulin regimen depending on major or minor surgery and glycemia status are required. Insulin (dose may need to be adjusted) is required, even if fasting, to prevent ketosis and DKA.
- Intravenous access pre- or intra-operatively is required to treat hypoglycemia.
- BGL monitoring at least hourly perioperatively is needed to detect and prevent hypo- and hyperglycemia. Urine or blood ketone measurements need to be performed if hyperglycemia >14 mmol/L (250 mg/dl) is present.
- In certain cases of minor elective surgery, youth can continue to receive insulin via CSII.

9 | MAJOR SURGERY (AS DEFINED ABOVE)

On the evening before surgery

- Give the usual evening and/or bedtime insulin(s) (some endocrinologists may recommend reducing the bedtime basal insulin amount by 20–30%). If on CSII, continue usual insulin basal rates (consider reducing basal at 0300 by 20% if there is concern about hypoglycemia).
- Monitor BGL and measure blood ß-hydroxybutyrate (BOHB) or urinary ketone concentration if BGL is >14 mmol/L (250 mg/dl).

Omit the usual morning insulin (short- and long-acting) on the day of surgery and start insulin infusion

- Start an iv insulin infusion and provide iv maintenance fluids consisting of 5% dextrose and 0.9% sodium chloride (see Appendices 1 and 2).
- Children on CSII should discontinue CSII insulin delivery when the insulin infusion is started.
- Depending on the placement of the CSII cannula in relation to the operation field, this can be left in place or may need to be removed
- Monitor BGLs at least hourly in the perioperative period. Aim to maintain BGL between 5 and 10 mmol/L (90–180 mg/dl) by adjusting the iv insulin dose or the rate of dextrose infusion during surgery.
- If BGL <4 mmol/L (70 mg/dl), give a bolus of iv 10% dextrose, 2 ml/kg; re-check BGL 15 min later and repeat if necessary. If still <4 mmol/L (70 mg/dl), stop iv insulin for 15 min and recheck.

- After surgery, when oral intake is not possible, the iv dextrose infusion should continue until the child is able to resume eating and drinking.

10 | MINOR SURGERY (AS DEFINED ABOVE)

Algorithms for different types of insulin regimens are suggested below.

For all insulin regimens—If the following occurs

- BGL <4 mmol/L (70 mg/dl)—give bolus of iv 10% dextrose 2 ml/kg; re-check BGL 15 min later and repeat if necessary.
- BGL >14 mmol/L (250 mg/dl) for >1 h—consider subcutaneous rapid-acting insulin using the child's usual correction factor or 5–10% of the child's usual total daily dose. Blood or urine ketones should be measured, and an iv insulin infusion considered if significant ketone production is present (most units consider serum ketones of >0.6 mmol/L significant).

1. People with diabetes treated with a regimen using multiple daily injections (MDI), twice or once daily basal (NPH, detemir, degludec or glargine) and rapid- or short-acting insulin

Morning operations

- On the morning of the procedure, give the usual dose of long-acting basal insulin (glargine, detemir, degludec) if usually given at this time. If preoperative evaluation shows a pattern of low BGLs in the morning, consider reducing the dose of long-acting insulin by 20%–30% (both doses if twice daily long-acting).[43] There is no evidence to inform the appropriate dose reduction of degludec; however based on the experience using other long-acting insulins a dose reduction of 20–30% on the day before surgery may be considered.
- In general, omit the usual prebreakfast rapid-acting insulin (e.g. insulin aspart, insulin lispro, and glulisine) until after the procedure, when it can be administered with a late breakfast. Consider rapid-acting insulin only to correct hyperglycemia.
- Consider commencing iv fluids: Individuals on an MDI regimen with BGL above target range may initially require iv fluids without dextrose. However, iv fluids with dextrose (5% dextrose/0.9% sodium chloride) should be started for everyone treated with NPH insulin to mitigate risk of hypoglycemia (because NPH insulin has a broad peak action). Alternatively, iv insulin infusion may be started as described above for major surgery.

Afternoon operations (if unavoidable)

- On the morning of the procedure, give the usual dose of long-acting insulin (if usually given at this time). For some individuals a 20–30% reduction of the dose will decrease risk of hypoglycemia.[43]
- If the anesthesiologist allows the child to eat a light breakfast and to consume clear liquids up to 4 h before the procedure, iv fluid administration (and iv insulin infusion, if applicable) could commence 2 h before surgery or no later than midday (see Appendices) if that is the diabetes team's choice of management.

2. Young people treated with continuous subcutaneous insulin infusion (CSII)

- In young people on CSII, this may be continued during a surgical procedure. However, if the anesthesiologist is not confident with CSII management, it is safest to remove the insulin pump and substitute an iv insulin infusion, as described above.
- When a child on CSII goes to the operating theater, it is important to secure the subcutaneous infusion cannula to prevent dislodgement and interruption of insulin delivery during the procedure. The insertion site should be away from the surgical field and in a non-compressible location. Ideally, the cannula should be changed the day before surgery and should not be in place for more than two days.
- If the general anesthesia is short (<2 h), CSII can continue to infuse insulin at the basal rate appropriate for the time of day. Basal rate can be suspended, if necessary, for no more than 30 min to correct any episodes of mild hypoglycemia.
- In case of hypoglycemia, dextrose should be administered (see above general recommendation)
- Do not give a bolus dose of rapid-acting insulin unless necessary to correct hyperglycemia and/or significant ketonemia as above.
- Consider commencing iv fluids: individuals with BGL above target range may initially require iv fluids without dextrose. An approach based on basal rate insulin titration may be more physiologic.[44,45] Alternatively, iv insulin infusion may be started as described above, instead of the CSII (make sure it is suspended or removed).
- Although advanced automated insulin delivery (AID) systems are available, there is no evidence on the perioperative use of these systems, and it is preferable to change to manual mode or iv insulin and suspend the AID during the operation.

11 | INTRAOPERATIVE CARE

- Surgical stress may cause hyperglycemia and increased insulin requirements. Regular BGL measurements at least hourly, and more frequently for hyper- or hypoglycemia (as described below), are recommended. If necessary, begin dextrose infusion or increase dextrose concentration of iv fluids from 5% to 10% to prevent hypoglycemia, or if an insulin infusion is initiated.
- Subcutaneous rapid-acting insulin may be used for minor surgery to maintain BGLs in the range 5–10 mmol/L (90–180 mg/dl). Rapid-acting subcutaneous insulin should not be given more often than every 2 h to avoid "stacking" and subsequent hypoglycemia.
- For major surgery or uncontrolled hyperglycemia during minor procedures, iv insulin infusion should be titrated to maintain BGL between 5 and 10 mmol/L (90–180 mg/dl) (Appendix A).

- If BGL exceeds 14 mmol/L (>250 mg/dl), urine or blood ketones should also be measured.
- If there is an unexpected acute drop in blood pressure, 0.9% sodium chloride is the preferred iv fluid and care should be taken to avoid fluids with potassium.

12 | POSTOPERATIVE CARE

After surgery, based on the young person's conditions, oral intake can restart, or iv dextrose infusion continued until food is tolerated. Similarly, based on the clinical conditions, either iv insulin infusion should be continued or short- or rapid-acting insulin (based on the usual insulin: carbohydrate ratio and correction factor) given, if needed, to reduce hyperglycemia or to match food intake. Insulin requirement may vary due to delayed oral intake, nausea, postoperative stress, additional medications, pain, and inactivity. For the first meal after surgery, it is preferable to give insulin after the oral intake, to make sure food is well tolerated without nausea or vomiting.

The young person's usual diabetes treatment regimen can be restarted, once they are able to resume oral nutrition.

13 | SPECIAL CIRCUMSTANCES

Emergency surgery

Most surgical procedures are elective, however, both minor and major surgical procedures may occur as emergencies. It is important to remember that DKA may present as an "acute abdomen" and, vice versa, acute illness may precipitate DKA.

Before emergency surgery in young people with diabetes, it is recommended to always check BGL, blood ketones (if available), or urinary ketones, serum electrolytes, and blood gases if ketone or BGLs are high.

If DKA is present, the ISPAD DKA protocol *(see ISPAD 2022 Consensus Guidelines Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State)* should be followed and surgery delayed, if possible, until circulating volume and electrolyte deficits are corrected and, ideally, until acidosis has resolved. If there is no DKA, start iv fluids and insulin management as for elective surgery.

T2D on oral medication alone

For young people with T2D treated with insulin, the same insulin guidelines as for elective surgery, depending on the type of insulin regimen, can be followed. For those on oral medications, the approach may vary based on the specific medication in use.

Metformin: the timing of discontinuation will depend on the expected length of the procedure. Metformin use has been associated with lactic acidosis, with risk increasing in the presence of renal insufficiency. As lactic acidosis is both a rare and life-threatening event, limited data are available to inform guidelines for perioperative management, and metformin may be useful in the postoperative hyperglycemic state.[46,47] Therefore, for major and minor surgery, metformin should be discontinued on the day of the procedure. For major surgery, metformin should be withheld for 24 h after surgery and until normal renal function has been confirmed. For minor surgery, metformin can be restarted after oral intake is tolerated.

Glucagon-like peptide (GLP-1) agonist: withhold on the morning of surgery.

All other glucose lowering drugs should be withheld on the morning of surgery.

Young people with T2D undergoing a major surgical procedure expected to last at least 2 h should be started on an iv insulin infusion as described above. For those undergoing minor procedures, it is advisable to monitor BGLs hourly and if greater than 14 mmol (250 mg/dl), treatment with subcutaneous rapid-acting insulin (0.1 unit/kg up to 10 units) no more frequently than every 3 h should be considered.

Young people with diabetes undergoing bariatric surgery

Individuals with T2D undergoing bariatric surgery may have significant improvement in insulin resistance and decrease in insulin needs shortly after surgery, even before weight loss occurs. Therefore, in these individuals, it is advisable to monitor BGLs closely after surgery and adjust insulin doses promptly. Interestingly, most remissions in adults occur almost immediately following operation, due to a dramatic increase in postprandial concentrations of the endogenous incretin, GLP1, mainly after Roux-en-Y gastric bypass.[48] These individuals are often on a clear liquid diet for several days after surgery and therefore the dose of basal insulin may need to be decreased to at least 50% of the preoperative dose. It is also suggested that the short-acting insulin dose be reduced postoperatively, starting with only half of the recommended preoperative dose if BGLs are elevated. Extended-release medications (such as metformin XR) should be converted to immediate release preparations after bariatric surgery.

Cystic fibrosis related diabetes (CFRD) on insulin

Young people with CFRD on insulin should receive the same perioperative management as those with T1D, including regular glucose monitoring and an individually tailored insulin regimen. Even though DKA may be uncommon in CFRD, testing for urine or blood ketones is suggested if BGL > 14 mmol/L (250 mg/dl).

14 | CONCLUSION

Surgery or general anesthesia in children and adolescents with diabetes should be performed in centers with appropriate personnel and facilities to support pre-, intra-, and post-operative care at the highest standard. Crucial to ensuring the highest level of safety is a careful liaison between the surgical, anesthesia and diabetes care teams before elective surgery and as soon as possible after admission for emergency surgery. Centers performing surgical procedures on young people with diabetes should have written protocols for postoperative management of diabetes on the wards where children are admitted.

CONFLICT OF INTEREST

The authors have declared no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Kapellen T, Agwu JC, Martin L, et al. ISPAD clinical practice consensus guidelines 2022: Management of children and adolescents with diabetes requiring surgery. *Pediatr Diabetes*. 2022;23(8):1468-1477. doi:10.1111/pedi.13446

APPENDIX A: INTRAVENOUS FLUID INFUSION GUIDE FOR SURGICAL PROCEDURES

A.1 | Maintenance fluid guide

A.1.1. | 0.9% Sodium chloride with 5% dextrose

- Major surgery and any surgery when basal insulin has been given
- If BGL is high (>14 mmol/L, 250 mg/dl), use 0.9% sodium chloride without dextrose and increase iv insulin; consider adding 5% dextrose when BGL falls below 14 mmol/L (250 mg/dl).
- Use maintenance rate (as outlined below).

A.1.2. | Sodium

There is evidence that the risk of acute hyponatremia may be increased when hypotonic maintenance solutions (i.e., 0.45% sodium chloride) are used in hospitalized children. Therefore, 0.9% sodium chloride should be used.

A.1.3. | Potassium

Monitoring of electrolytes perioperatively is recommended in young people with diabetes with unstable glucose levels. Potassium levels may become elevated, and use of potassium-containing iv fluids should be avoided intraoperatively to avoid a possible risk of excessive potassium administration in the event of emergency fluid resuscitation. Those undergoing more prolonged surgeries or emergency surgeries, during which metabolic decompensation is more likely, require intraoperative assessment of electrolytes and appropriate adjustment of the electrolyte composition of their iv solution.

A.1.4. | Example of calculation of maintenance requirements

	Body weight	Fluid requirement/24 h
For each kg between	3–9 kg	100 ml/kg/24 h (for 5 kg child: ~20 ml/h)
For each kg between	10–20 kg	Add an additional 50 ml/kg/24 h (for 10 kg child: ~40 ml/h)
For each kg over	20 kg	Add an additional 20 ml/kg/24 h

(Maximum 2000 ml/24 h female, 2500 ml/24 h male)

A.2 | Dextrose saline

The percentage is a mass percentage, so a 5% glucose/dextrose solution contains 50 g/L of glucose/dextrose or 5 g/100 ml. 1 (one) Unit of insulin generally disposes 5–10 grams of dextrose/h; 5% dextrose at a rate of 40 ml/h provides 2 grams dextrose per h, which will

require 0.1 to 2 units/h insulin (or as below for insulin infusion 0.025 U/kg/h insulin).[5]

APPENDIX B: INSULIN INFUSION

- Add soluble (regular) insulin 50 units to 50 ml 0.9% sodium chloride, making a solution of 1 unit insulin/ml; attach to syringe pump and label clearly as such.
- Start infusion as follows once BGL >4 mmol/L (>70 mg/dl)
  - 0.025 ml/kg/h (i.e., 0.025 units/kg/h) if BGL is <6–7.9 mmol/L (110–143 mg/dl)
  - 0.05 ml/kg/h (i.e., 0.05 units/kg/h) if BGL is between 8 and 11.9 mmol/L (144–215 mg/dl)
  - 0.075 ml/kg/h (i.e., 0.075 units/kg/h) if BGL is between 12 and 14.9 mmol/L (216—269 mg/dl)
  - 0.1 ml/kg/h (i.e., 0.1 units/kg/h) if BGL is ≥15 mmol/L (above 270 mg/dl)
- Titrate infusion by 0.01–0.03 units/kg/h to achieve BGL target range of 5–10 mmol/L (90–180 mg/dl).
- BGL must be measured at least hourly when the individual is on iv insulin. Increase to every 30 min after a change in therapy or every 15 min for BGL <5 mmol/L (80 mg/dl).
- Do not stop the insulin infusion if BG is between 5 and 6 mmol/L (90 mg/dl) as this will cause rebound hyperglycemia. Reduce the rate of infusion by 50%.
- The insulin infusion may be stopped temporarily if BGL <4 mmol/L (70 mg/dl) but not for more than 15 min.

Received: 27 September 2022 | Accepted: 8 October 2022

DOI: 10.1111/pedi.13432

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Management and support of children and adolescents with diabetes in school

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KEYWORDS: diabetes management, schools, type 1 diabetes, type 2 diabetes

1 | WHAT'S NEW/CHANGED

This chapter provides updated guidance on promoting optimal management of children and adolescents with diabetes within the school environment with a focus on those who require insulin. It includes details of educational resources to help school personnel provide support, encouragement, and supervision to students with diabetes, and specific details about nutrition and insulin administration. Updated recommendations on glucose monitoring, central to achieving optimal glycemic outcomes at school, include a focus on newer technologies such as continuous glucose monitoring (CGM) devices. These updates emphasize that a collaborative approach among parents, the student's health care team, and schools, together with advancements in communication and technology should be used to optimally support students for successful diabetes management at school.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

The following recommendations, reached by consensus, are largely based on expert opinion (E). They represent the ideal or best practice approach, recognizing that full implementation may vary geographically both within and between countries, and depending on availability of and access to resources.

2.1 | Terminology

Parent refers to a parent, legal guardian, or other person having responsibility for, or legal custody of, a child.

Child/children refers to individuals up to 19 years of age.

Medical team refers to the usual health care team treating the child with diabetes.

Diabetes educator refers to health care providers who specialize in the provision of diabetes self-management education for people with diabetes. This may include but is not limited to nurses, dietitians, nurse specialists, advanced practice nurses, physician assistants, certified diabetes educators, pharmacists.

School personnel refers to teaching and administrative staff, school nurses, and others who may be involved with the care of the student.

Diabetes management plan (DMP) is used as a general term for documents detailing the care required for the management of an individual student's diabetes while at school.

2.2 | Recommendations

- The number of young people with diabetes attending school is increasing (A), placing a significant burden on families, health care systems, and schools (E).
- Optimal management of diabetes, including at school, is a prerequisite for learning (B) and to avoid diabetes-related complications (A).
- Children may spend more than 30 h per week in the school environment. Maintaining normoglycemia during school hours is important. Glycemic targets during the time a child is at school should not differ from targets in any other setting (E).
- All students with diabetes must have an individualized plan that details the requirements for diabetes management. The plan must be developed and agreed on with parents in advance of school attendance (C). The plan should be reviewed and amended as and when necessary, according to the needs of the student, and/or at least annually (E).
- The type of insulin regimen used at school be tailored to the needs, ability, and wishes of the student/parent and should not be dictated by the availability of school resources (E).
- Parents cannot be expected to compensate for a lack of school resources and attend to their child's medical management during the school day (E).
- The World Health Organization and many common law countries recognize diabetes as a disability. Legal frameworks exist in many nations to ensure the child with a disability has equal opportunity to participate in all aspects of school life (A).
- Public policies and legislation to support students with diabetes in school should become the standard in every country. Governments must support schools with adequate resources to ensure they can provide the reasonable accommodations required to create a safe environment and facilitate optimal medical management as prescribed, allowing students with diabetes to participate in education on the same basis as their peers (C).
- Schools have a nondelegable duty of care to their students, and school personnel should take reasonable care to protect them from harm that is reasonably foreseeable. The expectation is that, irrespective of age and ability, all students with diabetes must receive the support, encouragement, and supervision of school personnel (E).
- Minimum reasonable accommodations include ensuring school personnel provide support as needed with insulin administration, blood glucose monitoring (BGM), and emergency management (E). Students with diabetes can be safely cared for in schools by a variety of trained personnel, including licensed (e.g., registered nurse) and unlicensed staff (e.g., teachers, education and special needs assistants, administrative staff, and so forth).
- Each school should identify trained and authorized school personnel to provide age- and developmentally- appropriate support for diabetes care during school hours (E).
- Lack of security for food, insulin, and glucose monitoring compounds the challenge of integrating diabetes self-care in the school setting, particularly in low-resourced countries. This does not negate the responsibility of policymakers and schools to ensure full school participation of students living with diabetes and to provide supportive and safe diabetes management in the school setting (E).
- All school personnel, including teachers, administrative staff, counselors, sports staff, nursing staff, and out-of-school-hours care staff, must receive appropriate diabetes education. Schools are responsible for adequately training their personnel about diabetes, but the content of the training is the responsibility of the health care team and parent (E).
- The medical team/parent must provide clear instructions for managing hypoglycemia (C). School personnel should be educated about the signs/symptoms of hypoglycemia, and a hypoglycemia emergency kit should always be with the student at school and off-site school-sponsored activities (E).
- Educational materials should provide information according to the level of contact staff have with the student with diabetes:

Level 1: Introductory education for all staff, ensuring a basic understanding of diabetes and of the emergency response plan for hypoglycemia;

Level 2: Intermediate education for staff with classroom or school-sponsored extracurricular contact, providing more detailed information around diabetes management and treatment of hypo- and hyperglycemia.

Level 3: Individualized skills training for staff providing direct diabetes care (E).

- Education resources are available in multiple languages to support diabetes awareness and knowledge in schools. These have been successfully implemented in both high- and low-resources settings (E).
- Care of the student must be individualized given variable experience, level of understanding, access to resources, coping skills, and economic circumstances of the student as well as varying roles and levels of diabetes expertise of school staff. Whether children can self-manage certain aspects of their diabetes and/or self-administer insulin is not necessarily age-dependent and can only be determined by the parent and health care team (E).
- Students with diabetes must be allowed to monitor their blood glucose (BG) levels, administer insulin, and to treat low/high BG values at any time during the school day, with adult supervision and assistance if needed (E).

- Administration, or careful supervision of insulin administration, by injections or insulin pump, requires school personnel to be specifically trained and legally authorized with informed parental consent (E).
- Glucose monitoring is central to achieving optimal glycemic targets at school. School personnel must know how and why to monitor glucose and be familiar with glucose monitoring devices (including glucometers and CGMs) (E).
- Access to food in schools is an integral part of enabling children to grow normally and balance their insulin and food intake. Managing nutrition during school hours, including calculating the carbohydrate content of school meals, is an important part of optimal diabetes management and requires collaboration between parent, the student, and school personnel (E).
- Students with diabetes must be enabled and should be encouraged to participate in physical activity. Adjustments for safety and optimal performance should be clearly outlined in the student's diabetes care plan (E).
- Successful diabetes management at school heavily depends on effective communication and problem-solving with the family (B). Schools should clarify expectations and coordinate communication (E).
- Young people with diabetes have a significantly increased risk of experiencing discrimination, stigma and bullying, all of which may affect self-esteem, motivation, and emotional health. Diabetes care tasks should be integrated into the student's regular daily routine as unobtrusively as possible to preserve their privacy, dignity and support their social and educational development (E).
- Some studies report higher rates of mental health disorders such as depression, anxiety, and eating disorders in young people with diabetes (B). Schools have a unique opportunity to identify and address mental health concerns in students with diabetes (E).
- Exams and other assessments are associated with stress and increased risk of acute transient episodes of hypoglycemia or hyperglycemia (B), which can affect performance (B) and require accommodation. Specific written arrangements should be in place (including access to BG monitoring equipment; fast-acting carbohydrates; and hypoglycemia emergency kit) for exams (E).
- The DMP is to be followed in school-based activities outside of regular school hours, including but not limited to before and after school programs, school camps, field trips, school related sports events (E).
- A collaborative approach between parents, the child's health care team and the schools, together with advancements in communication technology should be used to optimally support students for successful diabetes management at school (E).

3 | INTRODUCTION

Diabetes is one of the most common chronic medical conditions in childhood. Incidence rates of both type 1 and type 2 diabetes are increasing,[1–3] thus the number of young people with diabetes at school will continue to increase. Better glycemic management results in more optimal short- and long-term health outcomes.[4,5] Given that children spend a considerable proportion of their waking hours in school, failure to optimize diabetes management during this time contributes to suboptimal glycemic outcomes[6–8] and can increase the risk of diabetes complications. The effect of BG on learning is also important. Students with diabetes can achieve full participation in academic and extracurricular activities when diabetes is managed safely and effectively throughout the school day. Consistent and successful diabetes care at school will facilitate learning and social development, promote participation in all aspects of school life, and minimize absenteeism.[9,10] School personnel must be educated about diabetes and trained to support students, to meet contemporary standards of diabetes care, optimize learning, and create a supportive school environment.[11–16]

Everyday activities such as eating and physical activity affect BG levels, which can rapidly drop too low (hypoglycemia) or climb too high (hyperglycemia) outside of the target range. Attention to daily diabetes management at school can reduce the likelihood of these fluctuations. Knowing the risk of and how to respond to both hypo- and hyperglycemia and being vigilant about the potential dangers will help prevent severe blood sugar emergencies in the school setting.

These guidelines have been written with multiple stakeholders in mind, including students, parents, school personnel, and medical teams. Policy makers for health, education, and labor are also important stakeholders given that legislation can influence change and ensure minimal standards are established and met. Expectations for support in schools should be pragmatic and sustainable and must balance successful diabetes care, the student's right to be safe, supported and included, and the demands on school staff. Currently, many countries do not have legal or statutory provisions in place mandating that children with diabetes receive prescribed health care support at school. Because many jurisdictions do not have school nurses, the responsibility of insulin administration and BG monitoring falls on the family or on school personnel.[17,18]

While children may become technically skilled at an early age, students cannot be expected to be wholly responsible for their diabetes management at school, irrespective of their age and ability. All students with diabetes must receive support and encouragement from and be supervised by school personnel, especially when it comes to recognizing and treating hypoglycemia. Even older adolescents who usually self-manage their diabetes may have impaired judgment and cognition when their BG level is low.

Each student with diabetes must have a plan (sometimes known as a DMP) that includes individualized instructions for glucose monitoring, insulin administration and other aspects of diabetes care, and a detailed emergency plan. The parent/student, medical team and the school should agree on the plan, which should be reviewed and updated at least once a year or following any major life event or change in management. While terminology used for the various elements of the DMP (and the DMP itself) will vary from one jurisdiction to another, and the person completing tasks will differ based on the context, what is critical is that expectations, roles, and responsibilities are clear and that required supports are in place.

This chapter includes a review of the key essential resources and education required to support both the school staff and the student with diabetes. It outlines both minimal standards for low-resourced settings and optimal standards for all settings, respecting students' needs and rights as well as capacity of education and medical systems.

4 | DIABETES MANAGEMENT

4.1 | Insulin

The type of insulin regimen, injections, pump, or automated insulin delivery system should be tailored to the needs, ability, and wishes of the child with diabetes and their parents and may change over time as the child physically and psychologically matures. The optimal regimen provides insulin prior to each meal and snack (insulin pump or multiple daily injections). While insulin regimens that avoid lunchtime doses are still occasionally used, they are less flexible and make it difficult to balance insulin for lunch and snacks. The insulin regimen should not be dictated by school resources, but rather by the needs of the child and the availability of resources to manage diabetes (e.g., insulin; BG monitoring equipment).

Insulin pumps help facilitate optimal insulin delivery. They provide continuous basal insulin and require the user to manually enter the carbohydrate content of food consumed (meal bolus) and current BG (for corrections) prior to meals and snacks. The advantage of pumps at school is that manual injections are rarely needed. However, young students will need supervision or hands-on support to administer an insulin bolus for meals and snacks. While some pumps can automatically adjust basal and correction boluses according to the glucose levels from a connected CGM, these devices still require a manual bolus for food. In the future, it is anticipated that pumps linked to CGM will be able to automatically adjust insulin for food.

Every student with diabetes must be assured safe insulin administration at school. Designated school personnel have the responsibility to assist with insulin administration or, at least, to supervise and support the student doing it. Not all school personnel will agree to take on this responsibility; therefore, the school principal may ask for staff volunteers or designate staff members. School personnel require training by the health care team or by a parent. Medical orders and explicit informed consent and authorization by the parent for school personnel to give insulin to their child must be in place in advance for the protection and safety of the student and school staff (see Section 5). The key steps for insulin administration at school are: (a) determining the dose; and (b) delivering the insulin.

School personnel responsible for supporting students with diabetes should be trained to calculate insulin doses for those on injections. Parents must provide the carbohydrate counts for all foods, as well as the insulin-to-carbohydrate ratio and the correction factor or variable dosing scale. Insulin pens are recommended (rather than syringes) to promote earlier independence and to reduce the chance of dosage error.

Use of insulin dose calculators promotes earlier independent decision-making in young children.[19] Where available, bolus calculation can be facilitated using the "bolus advisor" feature on some commercially available home BG meters, approved smartphone apps or smart insulin pens, and is routinely available on pumps. Some students may use a fixed dose of insulin each day. Specific instructions regarding insulin administration and insulin dose adjustments at school should be incorporated into the student's DMP.

Premeal insulin should be given 10–20 min before eating[20] however, it can be difficult to apply this rule at school and for very young children.

4.2 | Blood glucose monitoring

Glucose monitoring is essential to achieving optimal diabetes management and must be supported in the school setting. BGM is necessary before insulin administration for safe and appropriate practice. The DMP should include glycemic targets, the frequency of BGM during the school day, and the method for monitoring (glucose meter, real-time CGM, or intermittently scanned CGM). At a minimum, BGM should occur before each meal, and before and after physical activity. Because both high and low BG levels may adversely affect performance,[21,22] BGM should also take place when the student is experiencing symptoms of hypo- or hyperglycemia and before or during school tests or exams.

The family is responsible for providing the BG meter/CGM and any related supplies (e.g., glucometer strips, lancets, batteries, and so forth). For students who cannot independently manage diabetes, school personnel should be trained to use the student's BG meter and/or respond to CGM alerts and alarms. The DMP should include instructions on when CGM values should be confirmed with a BG meter. Students using CGM at school should have a backup BG meter and supplies for use in the event the CGM stops working or falls off. All CGM supplies should be returned home with the student to avoid discarding durable device components such as transmitters. Students should have access to monitoring supplies at all times when at school and at school-sponsored events. Since CGM devices send data to a pump, a proprietary receiver, or a smartphone via Bluetooth®, students need access to these devices during class time. In addition, students should be able to charge BG meters and CGM readers/compatible smartphones as needed at school.

Recent advances in CGM technology include remote monitoring that allows parents to see their child's glucose levels and trends in real time. Studies suggest that when school nurses support CGM use[17,23] and when parents "follow" their children's CGM data parents have improved psychosocial outcomes, children have better glycemic outcomes[24,25]; and school nurses report feeling reassured. However, school nurses also reported concerns about more frequent phone calls, disrupted daily routines, and increased parental anxiety.[23] When students use CGM, parents and school personnel should discuss parental expectations, appropriate communication strategies and determine what is best for the student and feasible in the school setting to support successful diabetes management.[26]

4.3 | Nutrition in school

All children need a healthy, balanced diet for optimum growth and development, and education regarding healthy food choices and eating habits is part of diabetes management. For children with diabetes, nutrition is a key component of diabetes management that must be integrated into their treatment regimen and school routine while respecting cultural dietary restrictions and personal dietary choices.[27]

Carbohydrate counting is an essential part of diabetes management. Insulin dosing is based on the carbohydrate content of food so all students require access to reliable information about the carbohydrate content of their food. For "packed" lunches from home (prepared by parent), the carbohydrate content should be predetermined and provided by the parent. School-provided meals require cooperation between the school and the parent to determine the foods available and carbohydrate amounts based on portion size and nutritional content of foods served.

Access to food in schools is an integral part of enabling children to grow normally, exercise, and balance their insulin and food intake.[27] For children living with food insecurity, provision of food in school is essential. The 2020 World Food Program reported that one in two school children worldwide receive school meals daily, due in large part to growth of school-based nutrition programs in low-income countries. Effective school food programs increase children's access to school and improve learning.[27] Meals eaten in school may make up a large proportion of a child's daily nutritional intake[27] and for some children, may include breakfast clubs, snack times, and after-school clubs.

If school staff are not trained to administer insulin, this can create a barrier to accessing food supports like breakfast programs for students with diabetes.[28] Students who do not receive lunchtime insulin will require both a midday meal and snacks to prevent hypoglycemia and match the action profile of insulin injected at the beginning of the day (see Chapter 10, Nutritional Management in Children and Adolescents with Diabetes). Thus, the level of support required at school will vary depending on the student's regimen and level of independence, from ensuring the student consumes their meal on time, to assisting with counting carbohydrates to determine insulin doses.

Food choices in school may also be determined by local and national government policy, and issues such as obesity and dental health are also relevant for young people with diabetes. Where the student has a coexisting medical condition (e.g., celiac disease, cystic fibrosis) that requires additional dietary adjustments, these should be detailed in the DMP. Students with diabetes need access to snacks wherever they are, including in the classroom and during tests or examinations.

4.4 | Physical activity

All children and young people with diabetes should be given the same opportunities as their peers to safely participate in sports and physical activities, which offer physical health and social benefits. They should follow the same guidance for daily exercise—with respect to frequency, duration, and type of physical activity—as their peers without diabetes.

TABLE 1 Actions for the physical education instructor or coach

General considerations:
• Encourage all students with diabetes to participate in exercise and physical activities/sports. • Treat the student with diabetes the same as other students, except in meeting his or her medical needs (respect the student's right to privacy and confidentiality). • Make sure that BG monitoring equipment and an emergency kit for treating hypoglycemia is available at all activity sites and encourage the student to keep personal supplies readily accessible. • Encourage the student to always measure BG before exercise. • Know the signs and symptoms of hypoglycemia and hyperglycemia and be prepared to respond appropriately according to the student's DMP. • Communicate with the school nurse and/or trained diabetes personnel and parent regarding any observations or concerns about the student.
Management of hypoglycemia:
• Hypoglycemia can occur during and/or after physical activity. A change in the student's behavior could be a symptom of hypoglycemia. • Treat hypoglycemia immediately. Ensure the student waits until BG is back in target range before resuming activity. The DMP may suggest a snack following hypoglycemia if there is ongoing activity or more than an hour until the next meal or snack.
Management of hyperglycemia:
• Ketone levels should be checked if the student develops nausea and/or if BG levels are elevated above a given threshold as per DMP • Exercise is contraindicated if blood ketones are ≥1.5 mmol/L or urine ketone levels are 2+ or 4 mmol/L or greater. If ketones are between 0.6 and 1.4 mmol/L, the situation should be assessed prior to exercise. Correction with insulin is recommended.

The risk of hypoglycemia during and after exercise can be a barrier to physical activity.[29] The likelihood of hypoglycemia depends on many factors, including BG level prior to activity, when the student last ate or received insulin, individual sensitivity of BG to exercise, and the type, duration and intensity of activity. For instance, anaerobic activities or sprinting may cause the BG to trend upward while prolonged aerobic activities are more likely to cause a downward trend.

Regardless of the insulin regimen and technology used, students with diabetes need thoughtful planning to manage BG during and after physical activity. The DMP should include specific instructions for teachers, instructors, and coaches related to exercise.

Comprehensive recommendations are available in Chapter 14, Exercise in children and adolescents with diabetes. An overview with guidelines for the physical education instructor or coach are provided in Table 1.

4.5 | Hypoglycemia and hyperglycemia management in the school setting

Variations in BG levels outside of the target range are common in young people with diabetes and are the result of many different

factors including food intake, insulin, exercise, stress (e.g., caused by educational testing), and hormonal changes. Students with diabetes should wear a medical identification bracelet or necklace indicating the diagnosis to ensure appropriate intervention by emergency personnel if needed.

4.5.1 | Hyperglycemia

Hyperglycemia with a BG level above 10 mmol/L (180 mg/dL), should be avoided as much as possible for optimal health and learning. The ISPAD 2022 guidelines on glycemic targets (see Chapter 8 Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes) recommends a goal of over 70% of time in range (between 4 and 10 mmol/L [70 mg/dL and 180 mg/dL]). This should also be applied in the school setting. However, it is not uncommon for BG levels to rise above 10 mmol/L (180 mg/dL). This is usually not an emergency and should be evaluated as outlined in Table 2, and in most cases, students may remain in class if they are well.

TABLE 2 Hypoglycemia and hyperglycemia management in the school setting

Hyperglycemia: (BG above 10 mmol/L or 180 mg/dL)

- If student is *well*, encourage them to drink plenty of water and allow free access to the toilet
- Check ketones according to DMP or if the student develops nausea
- If student is *unwell* (altered mental status, vomiting, increased respiratory effort, or difficulty breathing) emergency services and parents should be immediately contacted

Hypoglycemia

Preparation/anticipation of hypoglycemia

- All school staff should be aware of the symptoms and signs of hypoglycemia and how to respond
- Emergency Care Plan available (outlines symptoms and management of hypoglycemia)
- Diabetes Emergency Kit should be readily available in the classroom/student's bag, containing a BG meter and fast-acting sugar (i.e., glucose tablets, sugar-containing drink) and a small carbohydrate snack

If student has symptoms of mild hypoglycemia

- Check BG immediately. If not possible to check BG and student has symptoms, assume hypoglycemia is present.
- If the BG is ≤3.9 mmol/L (70 mg/dL) treat immediately.
- Treat with fast-acting carbohydrate (i.e., fruit juice, glucose tablets, hard candy). The amount depends on the BG level, size of the student and the insulin regimen; this should be indicated in the DMP.
- Recheck BG in 15 min and repeat treatment if hypoglycemia persists
- Do not leave the student unattended until hypoglycemia has resolved.

If student has severe hypoglycemia (loss of consciousness and/or seizures)

- Place student in a "recovery" position
- Immediately place emergency call for assistance
- Do not administer anything by mouth
- Glucagon is recommended treatment (injectable or intranasal)

4.5.2 | Hypoglycemia

Mild hypoglycemia is the most common acute complication of diabetes, often occurring at least 1–2 times per week in those meeting glycemic targets. Therefore, hypoglycemia will happen at school and school staff need to be informed and prepared. Common symptoms of mild hypoglycemia include hunger, shakiness, sweating, pallor, irritability, dizziness which, if untreated, can progress to moderate hypoglycemia with weakness/fatigue, confusion. Severe hypoglycemia with loss of consciousness should be rare if hypoglycemia is promptly recognized and treated. A glucose value of <4 mmol/L (70 mg/dL) is an alert value that requires attention to prevent more serious hypoglycemia. A glucose value of <3.0 mmol/L (54 mg/dL) indicates serious, clinically important hypoglycemia. Attention to hypoglycemia alerts and the direction of arrows on CGMs should be observed and instructions should be provided in the DMP.

Detailed recommendations regarding hypoglycemia management are provided in Chapter 12 (Assessment and management of hypoglycemia in children and adolescents). Refer to Table 2 for management principles in the school setting. A student experiencing hypoglycemia must never be left unattended and must be monitored until the episode has completely resolved. If a student needs to leave the classroom to treat hypoglycemia, they should be accompanied by someone who can call for assistance if needed.

Once BG levels have been restored to normal, more complex carbohydrates (e.g., fruit, bread, cereal, or milk) can be provided to prevent a recurrence if the BG value was very low, if the student was physically active prior to the hypoglycemia episode or will be active before the next meal or snack. Hypoglycemia that occurs immediately before a meal should be treated first, and the subsequent meal-time insulin dose given only after the BG has normalized. Guidelines should be included in the DMP.

Severe hypoglycemia (loss of consciousness and/or seizures) can lead to injury and, in rare cases, death.[30] School personnel should have clear instructions for managing an episode of severe hypoglycemia. The student should be placed in a "recovery" position; nothing should be administered by mouth, and an emergency telephone call for assistance placed immediately.

Glucagon is the recommended treatment for severe hypoglycemia. Where appropriate/permissible, it is strongly advised that school personnel be trained to administer glucagon.[31,32] The requirement for an IM injection is a barrier to administration in many jurisdictions Other preparations, more recently introduced, which provide increased ease of administration include nasal glucagon (Baqsimi™) for children >4 years (A), dasiglucagon (ready to use pen for ≥6 years), analog and Gvoke™ (autoinjector for children >2 years of age). These latter preparations do not need to be mixed and can be successfully administered by untrained individuals making it a safe and feasible option for schools.[29,33] The school should notify parents every time a student has a severe hypoglycemic episode.

Strategies to prevent a hypoglycemia emergency at school include:

TABLE 3 Recommended content of the diabetes management plan (DMP)

Identification	Student's name, date of birth, parents' names, age of diagnosis, and type of diabetes
Contact information	Phone numbers of parents and student, diabetes physician/healthcare professional (HCP), and emergencies contacts
Monitoring	Times to measure, target ranges of glucose, preferred locations for measurement, CGM/isCGM information
Insulin treatment	Type of insulin and device (pen, syringe, pump), guidance to dose adjustments, and formulas/bolus calculator apps to calculate correction and carbohydrate doses
Hypoglycemia (low blood glucose)	Individualized symptoms, glucose levels that define need for intervention, and intervention instructions; situations that require emergency assistance; type of glucagon and instructions on its use
Hyperglycemia (increased blood glucose)	Individualized symptoms, glucose levels that define need for intervention, and intervention instructions; ketone monitoring
Food	Instructions for meals during participation in school-sponsored events, celebrations, field trips
Exercise	Changes to medication/monitoring/carbohydrate intake when participating in physical education and school-sponsored events
Self-care	Level of independence for monitoring and interpretation, insulin administration, carbohydrate counting, adjustments for exercise, technology management (e.g., pump site changes), and so forth.
Supplies	Medications, monitoring, snacks/rapid-acting glucose, glucagon rescue kit, back up supplies (infusion sets, syringes, and so forth). The DMP should clarify what supplies are provided and where they are stored
Support	Primary contact (parent, diabetes care team, other) for emergencies or when clarification to the DMP is required

- frequent BGM, particularly with activity;
- reacting quickly to signs of low BG; eating meals and snacks on time; and
- communicating with parents if there is a pattern of low BGs.

5 | DIABETES MANAGEMENT PLAN

Every student with diabetes will have an individualized treatment regimen and care plan. Some students need support all the time while others may be more independent. Accordingly, each student must have a DMP or medical orders to document a shared understanding between the student/parent and school for how their diabetes will be managed and who supports the student in school and extracurricular settings. Terminology and signing authority will depend on the local context. What is important is that the content exists and there is a mutual understanding of how the necessary supports will be provided for each student with diabetes.

The individual management plan should include the following elements:

Emergency response plan (ECP)—A concise action plan outlining how to recognize high and low BG levels and individualized treatment protocols for high and low BG levels and glucagon administration, if prescribed and available. Sample ECPs can be found in Appendix A.

Diabetes management plan—A formal and detailed document outlining the medical instructions for the individual student at school and specifying what diabetes responsibilities can or cannot be undertaken by the student based on the child's age, diabetes self-care knowledge, and cognitive maturity. The DMP should be provided by the student's parents, developed with input from the student (when appropriate), diabetes health care team, and agreed annually with the school principal or designate. The school should make reasonable accommodations to ensure the DMP can be delivered. The plan should be clearly documented and easy to implement and should not be changed without parental agreement. Recommended content is shown in Table 3. Sample DMP's from a variety of countries can be found in Appendix A.

The following additional plans or documents may be necessary and should be developed based on the DMP in partnership with the student, parent, and school personnel or the information can be included within the DMP.

Prescribed medication plan—Signed orders for the administration of medication (including insulin and glucagon) by designated school personnel should be provided by the Health Care Team and updated regularly. Given that insulin doses change frequently, and adjustments are often made at home by the parent, it may not be feasible to have updated signed orders from the prescribing practitioner. Signing authority for insulin dosing will be based on the setting and, in some contexts, the parent may be delegated to provide updated dosing guidelines for the school.

The self-carry form—This form gives a student permission to carry their diabetes supplies and self-administer insulin when necessary, during the day. This form can be incorporated into the DMP. In the US, this form is required and must be signed by the prescribing physician/HCP in order for a student to self-carry supplies and manage diabetes independently. This is not the case in many countries.

Accommodations plan—The accommodations plan is an agreement designed to ensure the student with diabetes has the same

access to education as other students. This is distinct from the content of the DMP which addresses specifics of diabetes management. It may be in the form of an individual health plan which would be developed by the school personnel in partnership with the student and parents. It may include provisions such as: having multiple school staff members trained to check BG; permission to eat whenever and wherever necessary, access to the water fountain and toilet without penalty; extra time during testing to monitor glucose and manage diabetes as needed; where diabetes supplies will be stored at school; contingency plan for school lockdowns and natural disasters.

Daily schedule—A single page document containing key information can be used as an in-class resource. This may include the daily schedule for BG checks and insulin, symptoms of and treatment for mild hypoglycemia, location of emergency kit, and thresholds for intervention with hyperglycemia.

6 | SCHOOL PERSONNEL—EDUCATION AND TRAINING

It can be difficult for parents of a student with diabetes to be confident that school personnel will know how to deal with all the issues related to the student's diabetes care. Similarly, from the school staff's point of view, supporting a student with diabetes may be daunting, especially if they have no previous diabetes-related experience. Empowering school personnel with knowledge and training about diabetes and the special needs of students with diabetes will help to overcome these challenges.[34] Each school must have a clear plan of how they will implement and maintain this education for school staff.

The following specific issues should be considered:

6.1 | Diabetes education and training of school personnel

The education and training of school personnel about diabetes needs to consider the following questions:

a. **Who provides the information?**

Parents of a student with diabetes should inform the principal and/or administration about their child's condition as soon as possible before starting a new school, school entry, or returning to school after a new diagnosis. Together, they should agree on a strategy to inform and educate teachers and other relevant school personnel. Parents are generally the first to deliver this information, but the child's diabetes health care team may also participate in this process.

b. **What resources should be used?**

School personnel should be directed to reliable, trusted, preferably endorsed, sources of information, and education about diabetes, and should be cautioned about seeking information from other sources. National professional diabetes societies and other affiliated parent associations often provide such resources (see Appendix A). To facilitate worldwide access to trustable information, the International Diabetes Federation (IDF) and ISPAD have developed an internet-based repository of educational materials, which is available in 10 different languages (see Appendix A). While terminology may vary, the fundamental content of the levels of education are recommended according to the level of contact with the student with diabetes, starting with level 1 and up to level 3 as indicated.

- **Level 1**: Introductory education for all school staff: A basic understanding of diabetes and how it impacts students. This includes recognition of low BG symptoms and signs and the urgency of treating hypoglycemia.
- **Level 2**: Intermediate education—for those interacting directly with students with diabetes in the classroom or other school based activities. This includes
- how and when to initiate treatment for high or low BG levels
- knowledge of the impact of food and activity on BG levels
- know and understand when and whom to call for assistance, including emergency responders, parents and medical team
- **Level 3**: Individualized skills training for delegated staff providing direct involvement in diabetes care, including:
- insulin administration
- insulin dose calculation
- insulin delivery devices including insulin pumps
- basic interpretation of BG monitoring results including CGM trends to support decision-making where applicable
- ketone monitoring
- glucagon administration

c. **How should the information and education be delivered?**

Delivery of information and education about diabetes to school personnel can be achieved using a variety of different formats and media. Face-to-face education sessions delivered by the diabetes health care team or the use of web-based "e-learning" education tools and provision of printed reading materials, either used alone or in combination, are the usual approaches. Specific education interventions have been developed and have been shown to be effective. Some national diabetes societies have also developed specific educational materials for schools. (See Appendix A).

Schools are responsible for ensuring that their personnel are adequately educated about diabetes and trained in the application of prescribed treatment for the individual student. The delivery and content of training is the responsibility of those parties responsible and accountable for the health of students: the parent supported by the treating diabetes health care team and the school administration. Training serves as a part of the informed consent process to enable parents to authorize school personnel to deliver medical care to their child on their behalf. It is the responsibility of the education system to facilitate this education for their staff and ensure they are provided

the necessary training. Optimally, there should be mandated/certified education for school personnel interacting with students with diabetes to ensure staff are trained and qualified with the necessary information and skills according to their level of involvement with the student.

d. **To whom should it be directed?**

Basic education (Level 1) of all school personnel is advocated. Anyone working at the school may encounter a student during a hypoglycemic episode and should be trained to recognize and respond. Level 2 education is mainly aimed at teachers, physical educators, other teaching assistants/aides directly supporting the student with diabetes, and nurses (where available). Level 3 training is required for those providing direct involvement in diabetes care. Provision of information to fellow students (and their parents) with consent can be very helpful and will facilitate inclusion and avoid potential discrimination. Students and families can be directed to useful information resources available on the internet. (Appendix A).

6.2 | Education regarding storage of supplies and medication administration

All teachers and school personnel must be aware that students with diabetes must have access to their devices, medication, and hypoglycemia treatment whenever needed. Ready access is especially important in situations such as natural disasters, lockdowns, and other emergencies.[35,36] Schools should have a safe place to store medication and supplies. Insulin vials should be stored in a refrigerator or at least in a cool room or insulated container, especially in hot climates. Insulin pens can be stored at room temperature (59–86°F, 15–30°C) for up to a month. Other supplies (e.g., BG meters, CGM sensors) should be kept in an easily accessible place. If school personnel are trained, glucagon should be readily available for treating severe hypoglycemia.

All students with diabetes should be provided with a safe and private place to perform BG checks and insulin administration. Insulin pumps should be with the student all the time, but if disconnected (i.e., during physical activity), insulin delivery should be suspended and the pump should be kept in a safe place that is also readily accessible.

6.3 | Nonmedical diabetes emergencies

Natural disasters, lockdowns, and other emergencies do occur in the school setting. As such, disaster preparedness is essential for all school settings. As noted above: storage of medication and supplies, and a disaster plan with contact information should be available for each student. Enough supplies should be available for each student for a minimum of 24 h. Parents should be responsible for providing and replenishing supplies for their child.

6.4 | Considerations for virtual school settings

Virtual schools, also known as online or cyber schools, relocate primary and secondary education to either an entirely home-based internet platform or a blended format with in-person schooling.[37]

There is some evidence that children with diabetes who attend school virtually may be at risk for suboptimal health outcomes. In one retrospective study that compared 87 youth with diabetes enrolled in virtual schools to age-, sex-, race-, diabetes type-, and diabetes duration-matched youth enrolled in traditional in-person schools, the virtual school students had higher mean HbA1c levels, lower insulin pump use, and more mental health conditions and were less likely to have recommended vision and dental evaluations.[38] Although prospective studies are needed to understand these associations, possible risk factors for virtual students may include a lack of supervised diabetes care, lack of social support, and lack of daily structure/routine including breaks for physical activity and healthy meals. Alternatively, an Italian study demonstrated an improvement in glycemic management during the COVID-19 pandemic lockdown.[39]

Students with diabetes who attend school virtually have the same legal rights as those who attend in-person. They should have a written DMP regardless of school learning mode. The American Diabetes Association Safe at School Campaign offers considerations to be included in the plan of a student with diabetes enrolled in virtual school. Many of these accommodations are the same as if the student were attending in-person school (e.g., permit breaks to leave the online classroom to use the bathroom without penalty; permit the consumption of food or drink during classroom time; and allow rescheduling of tests for hyper- or hypoglycemia). Others are unique to virtual school (e.g., permit student to turn off their camera to engage privately in diabetes self-care; agree upon a communication method, such as a chat box to alert the teacher of diabetes needs and care; record all online classroom sessions for later viewing).[40] Community resources (e.g., case managers) may be needed to support the virtual student in diabetes care during the day.

7 | SPECIFIC ROLES AND RESPONSIBILITIES

7.1 | Parents

Parents must communicate with school personnel shortly after their child's diabetes diagnosis, at the beginning of each school year, and whenever there are significant changes in the student's treatment regimen (e.g., starting a pump, CGM, or automated insulin delivery system).

The DMP should be developed in collaboration between the medical team and parent/student and agreed upon annually with the school to ensure that the student's needs are met. This should be signed by the parent/student and school with oversight from the

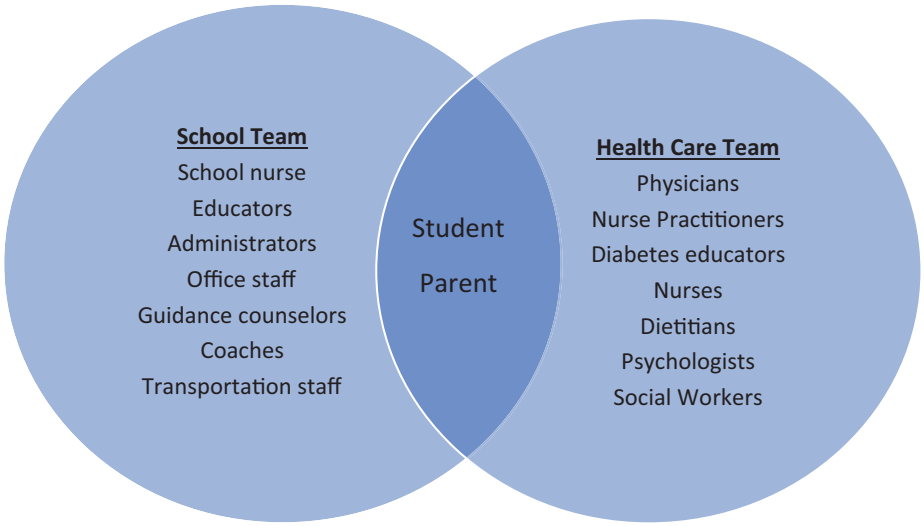

FIGURE 1 General overview of members of the student's diabetes care team. Ideally, the student and their parent should be part of both the school team and the health care team. Additional details regarding roles and responsibilities are provided in the text of the chapter.

medical team. Orders for the administration of medication in school must be signed by the medical team. By signing, the parents are providing consent to allow the school staff to implement the DMP.

Parents must supply all the necessary equipment and medication needed by the student at school. Contact numbers and addresses for emergency situations should be documented in the DMP. Parents are responsible for involving other family members who may assist in decision-making for the student's diabetes care.

A parent should not be expected to "fill the gap" of school resources and attend to their child's medical management during the school day. However, families may need to work with the diabetes care team to make specific individualized arrangements with the school. If school personnel cannot assume responsibility for performing or overseeing insulin administration, parents may believe the only option is to do it themselves. This has significant negative occupational consequences and financial burden, particularly for mothers,[41] and is not possible for many families. In one study, 47% of parents of younger children stated they were unavailable to attend school to administer insulin due to work and/or transportation challenges.[42]

7.2 | School team

The school team consists of any or all of the personnel listed in Figure 1, depending on the setting and the student's unique situation. School personnel are responsible for the safety and care of their students during school hours and school-sponsored activities. They should be supportive and attentive, respecting the student's right to participate in all activities and to perform glucose monitoring at any time. School personnel should be trained to help a student in need, for example, during episodes of hypoglycemia and hyperglycemia with illness. They may also need to perform, assist with, or supervise glucose monitoring and insulin administration. School personnel should also be made aware that variations in glycemia can interfere with attention and memory, as well as mood and behavior.[43–46]

7.3 | Health care team

The student's treating physician or nurse practitioner is responsible for prescribing medications and providing detailed instructions for glucose monitoring, insulin administration, management of hypoglycemia/hyperglycemia, and other aspects of diabetes care. The health care team (Figure 1) should provide input for the student/parent to develop the recommended DMP. In best practice the health care team will participate in or inform education and training for the school team and, with parental permission, be an accessible resource to provide ongoing support to the school.

Health professionals can also use clinical encounters to address diabetes management at school. Specifically:

- Ask about school challenges, especially related to diabetes, and the number of school days missed. Discussing these issues can help identify experiences of discrimination, stigma, or suboptimal care.
- Empower families to know their rights and to find policies or guidelines relevant to their jurisdiction.
- Keep a list of recommended tools and resources to educate and empower school staff about how to support students with diabetes and make these available to families with school-aged children (Appendix A).
- Provide support of a team member to assist families and to help educate school staff if needed or required.

7.4 | Student with diabetes

As children gain autonomy for their diabetes management, they can also assume some responsibility in the school setting. Specific responsibilities will vary based on the student's level of independence, desire, and motivation. There should be a gradual transfer of responsibility from adult supporters to the student, with the timing of these decisions at the discretion of the parent and health care

team and in partnership with the student. Regardless of the student's level of responsibility, parents should remain involved and engaged as part of the school and health care teams. Adolescents are less likely than primary (elementary) students to have a designated staff member and emergency treatment plan, to use pump therapy, and more likely to miss boluses at school.[42,47] Even students who are independent may need help with diabetes management when they are sick or experiencing hypoglycemia.

7.5 | Communication

Parents, students, and members of the school and health care teams should work together at the beginning of and throughout the school year to negotiate and coordinate communication expectations. Schools should identify a key member of the school team who will be primarily responsible for communicating with parents, ensuring that the DMP is carried out accurately and that other school personnel receive adequate training. Students should be involved in informing and educating their teachers and coaches about their diabetes. Typically, parents are the liaison between the school and health care teams. However, these teams may communicate directly when parents cannot be reached or if there are concerns about the health and safety of the student.

7.6 | Policymakers

Policymakers (e.g., on school boards or regional/national governments, depending on the jurisdiction) are responsible for ensuring that policies related to managing diabetes in school exist, are followed, and are kept current. They should also ensure that students with diabetes and their families have clear pathways to follow if schools or school boards are not providing the required support, or if the health/safety of a student is compromised in any way.

8 | PSYCHOSOCIAL AND NEUROCOGNITIVE CONSIDERATIONS

8.1 | Glycemic excursions and learning

Both hypo- and hyperglycemia may acutely impact children's cognitive abilities and these effects may persist once the BG level is back in the target range.[43] Hypoglycemia may impede learning and the ability to sustain attention, think critically and solve problems, and be associated with feelings of anxiety, restlessness, or low energy.[43,48,49] Children may also experience hypoglycemia unawareness, preventing them from treating the low glucose level in a timely fashion or making their needs known to others. Children experiencing mild to moderate hypoglycemia may be reluctant to report their symptoms to a teacher due to fear of embarrassment or social stigma. When any of these situations occurs, the student's cognitive acuity may be impacted and they may not be able complete tasks or retain information that is being taught.

While there is no firm evidence that acute hyperglycemia adversely affects cognition during school, related symptoms such as reduced energy and general malaise, plus frequent trips to the bathroom may make it difficult for children with diabetes to achieve optimal academic performance.

Every effort should be made to reduce and mitigate hypo- and hyperglycemia so that students with diabetes are not removed from their learning environment.

School personnel must allow students to monitor their glucose levels (via CGM or BGM) frequently and to take action to return BG to the target range.

8.2 | Neurocognitive complications

There is considerable evidence that some children with diabetes may experience lasting impairments in their skills and abilities linked to how their brains function.[44] Frequent episodes of severe hypoglycemia, prolonged hyperglycemia, and diabetic ketoacidosis (DKA) at diagnosis may be causes of these effects, and children diagnosed with diabetes at a very young age may be at higher risk.[50] Few studies have included measures of academic performance to determine how neurocognitive impairments affect school functioning in students with diabetes. However, a recent study found that an increasing HbA1c trajectory during high school was associated with a lower grade point average.[45] Maintaining children's glucose levels within the target range of 4–10 mmol/L (70–180 mg/dL) as much as possible will help avoid long-term complications, minimize diabetes burden, enhance quality of life, and enable the student to achieve their potential. Children with diabetes who experience frequent or pronounced glycemic variability may benefit from periodic neuropsychological evaluations if appropriate referral sources are available. Cognition may be impacted for 30–60 min following an episode of hypoglycemia and accommodations during exams or assessments may need to be made on a case-by-case basis.

8.3 | Psychological adjustment

There is evidence to suggest that young people with diabetes have a greater incidence of mental health disorders compared with their peers without diabetes.[46] Some studies show that the rates of depression and anxiety are two times higher for adolescents with type 1 diabetes.[51] Adolescents with type 2 diabetes (T2D) are also at increased risk for psychological problems, including self-esteem and body image concerns, depression, anxiety, and behavioral problems.[52,53] Disordered eating and behaviors to control weight (e.g., insulin omission) are common in young people with type 1 and type 2 diabetes.[54] Although few studies have examined the link between psychological problems in children with type 1 diabetes and academic outcomes, a small, cross-sectional study found higher depression scores were associated with poorer academic performance.[55]

Both parents and students report concern about hypoglycemia at school, especially during physical activity,[56] and fear of hypoglycemia is common.[57–59] Children and/or their parents may engage in potentially negative health behaviors to prevent hypoglycemia, such as taking less insulin than needed or overeating.[52] The connection between fear of hypoglycemia and school performance has not been studied. However, symptoms of acute hyperglycemia (diminished energy, general malaise) that may result from trying to prevent hypoglycemia may affect school performance. Since fear of hypoglycemia is more common in young people with anxiety,[60,61] school avoidance behaviors such as attempting to stay home, leave school, or go to the nurse's office may be especially common. Fear of hypoglycemia in school personnel has not been formally studied, but clinical experience suggests that teachers may also have concerns about hypoglycemia when they are the only adult in the room capable of treating it. Teachers should be encouraged to discuss their concerns with the student's parent, and be trained to recognize and treat hypoglycemia.

Schools provide an opportunity to identify and treat psychological challenges in young people with diabetes. Educational interventions for school personnel should include the mental and physical burden of diabetes self-care on young people and their increased risk for mental health disorders. Once educated, school nurses, guidance counselors, and other personnel can serve as a bridge to community mental health resources.

8.4 | Family influences

When younger children are not in school, the burden of diabetes management falls almost exclusively on parents. In early adolescence, the transfer of responsibility from parent to child begins, but requires a delicate balance of fostering the young person's growing independence while maintaining engagement in diabetes care. Longitudinal studies suggest that when parents give up responsibility too early, adolescents are less engaged in diabetes self-care and glycemic levels become suboptimal.[62] Thus, regardless of the age of the child, diabetes management depends heavily on family communication, problem-solving, and supportive parental involvement.

In general, studies suggest that both parents and school personnel perceive a lack of communication about diabetes care in the school setting. Parents have varying preferences for communication frequency and format, with some requesting daily (or more frequent) phone/text interaction and others simply requesting copies of weekly or monthly BG logs. Schools should work with families at the beginning of each school year and as needed to negotiate and coordinate communication expectations. School personnel should be aware of "red flags" related to a lack of parental involvement in diabetes care, such as minimal communication, running out of diabetes supplies in the school setting, chronic hyperglycemia, as well as frequent school absences and hospitalizations. If these concerns are noted, school personnel should notify the child's diabetes health care team so they can follow-up with the family.

8.5 | Peer influences

Research indicates that adolescents with T1D have difficulty engaging in diabetes self-management tasks around peers due to fear of judgment and concern about social acceptance.[63] Peer relationships may also affect diabetes outcomes.[64-66] A recent systematic review revealed a scarcity of literature on peer victimization and bullying in children with diabetes, but in the few available studies, children with T1D report greater levels of peer victimization than their peers without T1D, and bullying was associated with higher HbA1c levels.[63] School personnel should be aware of peer influences and facilitate referrals to guidance counselors or outside mental health providers as needed.

8.6 | Socioeconomic influences and health disparities

Children from underserved communities face competing priorities related to socioeconomic status and social environment, putting them at risk for adverse health, psychosocial, and academic outcomes. Challenges may include food insecurity, lower parental educational levels, diminished self-efficacy for school success, more frequent absences, more frequent changes of schools during the academic year, and reduced access to materials such as paper, pens, pencils, computers, and internet access. When these students have diabetes, the daily demands of managing the condition are an additional stressor and can result in higher HbA1c levels, more frequent episodes of DKA, and earlier onset of complications.[67] Youth from racialized communities also experience decreased access to diabetes devices.[68,69]

When a student with diabetes faces socioeconomic obstacles on multiple levels, timely, appropriate, and concerted interventions are critical to prevent health and academic disparities. Health care providers, teachers, and school personnel should be even more attuned to the academic needs and circumstances of children with diabetes from lower resourced groups.

9 | LEGAL ISSUES, PUBLIC POLICY, AND RIGHTS OF STUDENTS WITH DIABETES

Diabetes is recognized in common law as a disability.[70-73] The United Nations Convention on the Rights of Persons with Disabilities recommends that "effective individualized support measures are provided in environments that maximize academic and social development, consistent with the goal of full inclusion."[74] Legal frameworks exist to protect children and adolescents with diabetes to ensure the student has an equal opportunity to participate in all aspects of school life. Other legislation that is not specific to diabetes care in school can also be referenced to secure care for students.[75-78]

Discrimination occurs when a person with a disability is treated less favorably than a person without the disability in the same or

TABLE 4 Key messages for less resourced countries

- Children with diabetes should not be limited in what they can do, and should be able to attend school, participate in activities, receive an education, and live happy, fulfilled lives.
- Most schools are supportive; however, a student's nurse or doctor can visit the school to explain diabetes and its management in a clear and concise manner, or a parent might feel confident enough to do this themselves with support from the local health care team. Such visits and contact with the school and the health professional can be extremely encouraging to parents and students.
- A simple individualized diabetes management plan for the student with diabetes is a good guide for the teacher to follow day-to-day at school. This should include step by step instructions for management of emergencies and contact details of parents.
- Students with diabetes should be allowed to monitor their BG level as necessary depending on the availability of glucose strips.
- It is always preferable for the child to receive prelunch insulin; a safe, private place is required for them to give their injection at school.
- A refrigerator or cool place/container (e.g., clay pot) is required for storage of insulin particularly in hot climates.
- School personnel should be educated on the management of hypoglycemia, and parents should ensure that appropriate treatment and retreatment is available at the school. Emergency assistance should be called if the student is unable to eat or drink to treat the hypoglycemia.
- School personnel need to be aware that prior to and during physical activity the student with diabetes may need to eat or drink carbohydrate containing foods to avoid hypoglycemia.
- When BG levels are high, students should be allowed to drink water and use the toilet as necessary.
- Teachers should be aware that other children may tease the student with diabetes. A simple explanation to classmates is encouraged (IDF).
- Teachers should also understand the classic symptoms of T1D, so they can identify undiagnosed children in the future. It is not uncommon for T1D to be mistaken for malaria, appendicitis, gastroenteritis, or pneumonia.

similar circumstances.[70-73] Discrimination is unlawful in many countries when it occurs in an area of public life such as in school. Children with diabetes have a significantly increased risk of being exposed to discrimination. This can have an impact on self-esteem and cause feelings of stigmatization and fear of being different from their peers.[7] Schools in most countries are obliged by law to make "reasonable adjustments" to facilitate prescribed medical care to allow for students with diabetes to participate in education on the same basis as their peers. This should become the standard in every country despite challenges in less-resourced countries. In countries where legislative protections to support students with diabetes are not expressly defined, ISPAD advocates that those students be allowed to attend school in a safe and supportive environment that enables best practice of the management of diabetes.

Schools have a nondelegable duty of care to their students and staff to take reasonable care to protect them from harm which is reasonably foreseeable. There are obvious foreseeable risks associated with not providing appropriate management of diabetes. School personnel have a duty of care to the child with diabetes to appropriately manage the effects of low and high BG levels according to parent and health care team instructions. Staff require training in administration of glucagon as a rescue medication when prescribed and included in the DMP. Duty of care does not extend to automatically having authorization to administer medication including insulin or injectable glucagon or to undertake invasive procedures.

Informed consent is a person's voluntary decision about medical care, including diabetes self-care, that is made with knowledge and understanding of the benefits and risks involved. Only the parent or legal guardian in the case of a minor can provide informed consent. The child's DMP requires the informed consent of the parent and must be signed by the parent. All information, risks and associated circumstances must be disclosed to the parent to ensure that their consent is valid.

Policies, whether at a national, regional or school-board level, should be developed in collaboration with diabetes health professionals, families of students with diabetes, educators, and school administrators. These policies must support the training of school staff to meet their duty of care and ensure the student's safety and ability to fully participate in school and school activities. This training needs to be specifically resourced by the education and healthcare sectors.

Despite the availability of guidelines and training resources addressing diabetes management at school,[13,14,79–84] many families continue to report experiences of inadequate support leading to suboptimal care (e.g., lack of access to insulin during the school day), stigma and discrimination, exclusion from school activities such as field trips, or other negative events.[9,10] Documented barriers to achieving effective diabetes management at school include lack of formal education or training for school staff, lack of clarity about roles and responsibilities, and misconceptions or fears about supporting students with diabetes.[10,85]

An example of a legislative approach is the 2009 Swedish law that secured the rights of students with special needs, including diabetes.[6] The Swedish law required a detailed agreement on how school personnel will support the student's needs during the school day, with training provided by the student's diabetes team. National surveys conducted before[7] and after[8] this legislation showed improvement in glycemic outcomes and an increase in the proportion of children receiving support from a designated school employee.[6] A recent survey in British Columbia, Canada, a province with a legislated school policy, demonstrated strong agreement from families and program coordinators alike that the care plan is meeting both safety and diabetes management needs.[86] The formal obligation to support diabetes care at school in these jurisdictions goes beyond the many recommendations, policies, and guidance documents that exist in other countries and demonstrates potential benefits to students with diabetes in adopting a national or regional policy approach.[87]

Measures to evaluate and/or improve compliance with legislation or public policy are not well described in the literature but are critical to ensuring equity for students with diabetes. This is especially true in lower resource areas, with limited opportunities to know if guidelines are followed, given basic challenges faced by students with diabetes in these settings. Evidence suggests that students with diabetes can be safely cared for in schools by a variety of trained personnel,

including licensed (e.g., registered nurse) and unlicensed staff (e.g., teachers, education and special needs assistants, administrative staff, and so forth).[18,88]

An effective diabetes-in-school policy starts with the requirement for a DMP that describes the student's daily care needs and instructions for handling nonstandard situations. Recognizing the wide variability globally in access to technologies and to school-based medical and nonmedical support staff, at a minimum, policies should address three essential components of diabetes care at school and related training needs of school staff or others who will provide support to students:

- Access to insulin
- Glucose monitoring
- Emergency management

It is also recommended that, given the ongoing new developments in diabetes technology and management, policies on diabetes-in-school should be revisited and updated regularly.

In all countries, parents and health care teams should seek to establish a supportive, collaborative, relationship with the child's school team and tailor the training to the child's individual needs, thus enabling school personnel to understand why certain medical interventions are important for the individual child. It is critical that all school personnel who will interact with the child with diabetes receive the necessary training. The person(s) acting as the parent's agent for insulin administration should be named in the students' DMP.

Through advocacy, diabetes health professionals can help bring about policy change. National or regional diabetes associations (e.g., Diabetes UK, Diabetes Canada, American Diabetes Association, Diabetes Australia, Swedish Diabetes Association [Svenska Diabetesförbundet], IDF, ISPAD, JDRF, and so forth) are natural partners for this work (Appendix A). Diabetes care team members, parents, students, and school personnel are encouraged to become involved in efforts to establish policy where none exists, improve policy that is inadequate, and enforce policy where implementation is not universal and equitable.

10 | DIABETES IN SCHOOLS IN LOW AND MINIMALLY RESOURCED COUNTRIES

In less-resourced settings sending children to school may be compounded by other issues such as lack of insulin, diabetes supplies, food insecurity, transport challenges, and local conflict and war. School is a time of learning, making friends, having fun, and finding peer groups. However, for children with diabetes, this can instead be a time when they are excluded, isolated or stigmatized. As health and school professionals, we must advocate that children and youth with diabetes receive the same educational and extracurricular opportunities as other children in their community, and equal opportunities for ongoing education and fruitful employment (Table 4). The limitations in less resourced countries are recognized but should not be an excuse to limit or exclude students with diabetes from full participation in school activities.

The International Diabetes Federation (IDF e-Library) "Life for a Child" initiative has developed an education website that includes multilingual resources for schools.[73] In addition, the IDF "Kids and Diabetes in School" project tackles diabetes (including types 1 and 2 diabetes, and healthy food choices and lifestyle advice) management in school with visual materials, coupled with an education program for school personnel, parents, and students.[89] This project was successfully trialed in Brazil[34] and India[90] and is now available in 18 languages (see Appendix A).

11 | CONCLUSION

Students with diabetes must have the same access to education as other students, in a safe and supportive environment that enables them to successfully manage diabetes, while empowering the school system and staff with the knowledge and tools to assist them. Legislation has been passed in some countries and is important to ensure equitable access to supports. Several excellent resources have been developed to educate school staff and are freely available (see Appendix A). There are differences between countries regarding legislation and the availability of personnel and diabetes supplies and technology.

At the most fundamental level, each student with diabetes requires access to insulin, glucose monitoring, and emergency treatment of hypoglycemia. All staff need to be aware of the symptoms and initial management of hypoglycemia. Each school should identify actively involved school personnel to provide age and developmentally appropriate support for diabetes self-care during school hours. Students living with diabetes should have ready access to advanced treatment strategies for diabetes including intensive insulin therapy and glucose monitoring technology and the school should not be a barrier to these treatments. Both hypo- and hyperglycemia affect not only the long-term risk of diabetes complications, but also affect learning, behavior, and cognitive functioning. Striving for normoglycemia is a cornerstone of modern diabetes care and schools are an essential partner in achieving this goal.

These guidelines emphasize the importance of communication and collaboration between the multiple stakeholders with a common goal of support, safety, and inclusion at school for students living with diabetes.

AUTHOR CONTRIBUTIONS

All authors contributed to literature review, writing designated sections of the guidelines, consensus discussions, review and revision of the manuscript. SL prepared first draft. Final revision by SL and FM.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13432.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Lawrence SE, Albanese-O'Neill A, Besançon S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Management and support of children and adolescents with diabetes in school. *Pediatr Diabetes*. 2022;23(8):1478-1495. doi:10.1111/pedi.13432

APPENDIX A

A.1 | LINKS TO ONLINE RESOURCES RELATED TO DIABETES IN SCHOOLS

The goal is for this to be a live document that can be updated over time as resources are created or updated.

A.2 | NATIONAL WEBSITES RELATED TO DIABETES IN SCHOOLS

IDF Kids and Diabetes in Schools 2019 (Multilingual resource available from: kids.idf.org) https://www.idf.org/e-library/education/73-kids-diabetes-information-pack.html.

American Diabetes Association https://www.diabetes.org/tools-support/know-your-rights/safe-at-school-state-laws/training-resources-school-staff

Canadian Pediatric Society: Diabetes at School https://diabetesatschool.ca/

Diabetes Australia: Diabetes in Schools. https://www.diabetesinschools.com.au/

Diabetes UK: Diabetes in Schools https://www.diabetes.org.uk/guide-to-diabetes/your-child-and-diabetes/schools.

Turkey: https://okuldadiyabet.com/

A.3 | EDUCATIONAL TRAINING MODULES FOR SCHOOL STAFF

JDRF Educational Video A short video narrated by students with diabetes that explains life with type 1 diabetes (T1D) to extended family, parents, teachers, coaches and fellow students. https://www.jdrf.org/t1d-resources/living-with-t1d/school/

Life for a Child: Education and Training Resources https://lifeforachild.org/education/

American Diabetes Association Training Resources for School Staff https://www.diabetes.org/tools-support/know-your-rights/safe-at-school-state-laws/training-resources-school-staff

Canadian Pediatric Society: Managing type 1 diabetes at school: An online course for educators and school staff. https://diabetesatschool.ca/schools/managing-type-1-diabetes

Diabetes Australia: Training and Support - Diabetes in Schools https://www.diabetesinschools.com.au/training-and-support/

Diabetes Committee of the Australian Pediatric Society e-learning module for schools: https://www.t1d.org.au/

Diabetes UK: Diabetes in School Resources https://www.diabetes.org.uk/guide-to-diabetes/your-child-and-diabetes/schools/diabetes-in-schools-resources

A.4 | SAMPLE DIABETES MANAGEMENT PLANS

Australia:

Diabetes Australia (state specific plans) https://www.diabetesinschools.com.au/resources/diabetes-management-plan-principal/

Diabetes Committee of the Australian Pediatric Society Diabetes Action and Management Plans: https://www.t1d.org.au/

Canada: https://diabetesatschool.ca/tools/individual-care-plan

UK: https://www.diabetes.org.uk/guide-to-diabetes/your-child-and-diabetes/schools/diabetes-in-schools-resources

USA: ADA Diabetes Medical Management Plan https://www.diabetes.org/dmmp

A.5 | OTHER MANAGEMENT PLANS

ADA

Section 504 Plan The 504 Plan sets out an agreement to make sure the student with diabetes has the same access to education as other children.

https://www.diabetes.org/tools-support/know-your-rights/safe-at-school-state-laws/written-care-plans/section-504-plan

Hyperglycemia Emergency Care Plan https://www.diabetes.org/sites/default/files/2019-06/hyperglycemia%20emergency%20care%20plan.pdf

Hypoglycemia Emergency Care Plan https://www.diabetes.org/sites/default/files/2019-06/hypoglycemia%20emergency%20care%20plan%20for%20low%20blood%20glucose.pdf

Guidelines for Continuous Glucose Monitors (ADA Safe at School): https://diabetes.org/sites/default/files/2022-03/CGM-3-15-22.pdf

Diabetes Disaster Preparedness Plan 2018 (Available from: www.DiabetesDisasterResponse.org)

ADA. Safe at School: Recommendations for Virtual Learning 2020 (Available from: https://www.diabetes.org/sites/default/files/2020-09/Covid19virtuallearningrecs09.29.2020.pdf)

A.6 | POLICIES/POSITION STATEMENTS

ISPAD Position Statement on Type 1 Diabetes in Schools (2018) https://www.ispad.org/news/news.asp?id=420540

Canadian Pediatric Society: Managing type 1 diabetes in school: Recommendations for policy and practice (2015) https://cps.ca/documents/position/type-1-diabetes-in-school

UK Education UDf. Supporting pupils at school with medical conditions 2014 (Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/803956/supporting-pupils-at-school-with-medical-conditions.pdf).

USA American Association of Diabetes Educators: Management of Children with Diabetes in the School Setting - AADE Position Statement https://www.diabeteseducator.org/docs/default-source/practice/practice-resources/position-statements/diabetes-in-the-school-setting-position-statement_final.pdf

UK Sample Medical Conditions Policy for School: Type 1 Diabetes (2018) https://www.diabetes.org.uk/resources-s3/2018-11/1201BD_Sample%20medical%20conditions%20policy_DIGITAL.pdf

A.7 | OTHER ADVOCACY TOOLS

Life for a Child. DKA Prevention Posters 2018 (Available from: https://lifeforachild.org/education/dka/).

Type 1 diabetes at school: Rights and responsibilities from the Canadian Pediatric Society (video 2:58) https://youtu.be/jWGapJ2ymLo

Starting Secondary School with Type 1 Diabetes (video 3:42) https://www.youtube.com/watch?v=kcwGo54tzbo

From US NIH/NIDDK Tools for diabetes in school. https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/diabetes/helping-student-diabetes-succeed-guide-school-personnel

US laws and diabetes in school. https://www.diabetes.org/tools-support/know-your-rights/safe-at-school-state-laws

Sanofi Turkey: Creating Awareness on Diabetes at School https://www.youtube.com/watch?v=9Xd4-lQUXHU

A.8 | FOOD STANDARDS

KiDS Educational Guide on Diabetes and Nutrition in School https://idf.org/e-library/education/148-educational-guide-on-nutrition-and-diabetes-in-schools.html

United Kingdom: Education Df. School Food Standards Guidance UK (2015, updated 26 August 2021).

http://www.schoolfoodplan.com/wp-content/uploads/2015/01/School-Food-Standards-Guidance-FINAL-V3.pdf.

USA: There are state and federal requirements in the US to provide nutrition information for food prepared at school. Here is an example of nutrition content for a county's school district in Florida. You can zero in on School, day, meal, exact content. This is widely used by school staff and families. https://sbac.nutrislice.com/menu/menus-eula

Received: 29 September 2022 | Accepted: 30 September 2022

DOI: 10.1111/pedi.13427

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes | WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Managing diabetes in preschoolers

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1 | SUMMARY OF WHAT IS NEW OR DIFFERENT

- Preschool children with type 1 diabetes (T1D) who have access to modern diabetes care can safely achieve a HbA1c below 48 mmol/mol (6.5%).
- Continuous glucose monitoring (CGM) is the recommended tool for glycemic monitoring in preschoolers with T1D.
- When using CGM, a reasonable treatment target is 50% time in target (TIT) 3.9–7.8 mmol/L (70–140 mg/dL) or 70% time in range (TIR) 3.9–10 mmol/L (70–180 mg/dL).
- Insulin pump is the preferred method of insulin delivery in this age group whenever available and affordable.
- Hybrid closed loop insulin pump therapy is valuable and needs to be made available to children with T1D in this age group as they generally have a high day-to-day variation in insulin needs.
- Early onset diabetes is associated with a high lifetime risk of diabetes complications, necessitating optimal glycemic control from onset.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- The ISPAD target hemoglobin A1c (HbA1c) for children is <7% (<53 mmol/mol). As children diagnosed with T1D at preschool age are expected to have a long diabetes duration and thus have a high risk

of diabetes complications **B**. They benefit from a tight glycemic target and maximizing time spent in glycemic target range from the onset. **C**

- A reasonable treatment goal after the initial remission period in insulin treated children younger than 7 years can be >50% of time in target (TIT) 3.9–7.8 mmol/L (70–140 mg/dL) or >70% TIR 3.9–10 mmol/L (70–180 mg/dL). **B** Soon after diagnosis, during the remission period, a higher TIT and TIR is preferable. **E**
- Intensive insulin therapy, that is, as close to physiological insulin replacement as possible, with a combination of basal insulin and pre-prandial insulin boluses should be used, with frequent glucose monitoring and meal-adjusted insulin regimens. **C**
- Insulin pump therapy is the preferred method of insulin administration for young children (aged <7 years) with T1D whenever available and affordable. **E**
- As pump treatment develops further with hybrid closed loop (HCL)/automated insulin delivery (AID) this treatment modality needs to be made available and adapted for children younger than 7 years. **A** The special needs of toddlers and preschoolers should be addressed when developing these devices. **E**
- If pump therapy is not available, multiple daily injections (MDIs) should be used from the time of diagnosis. **E**
- Pre-prandial administration of bolus insulin and insulin given for correction if blood glucose is high is preferable to giving the insulin dose during or after the meal. **B**
- Studies in this age group support introducing carbohydrate counting at onset of diabetes. **C**
- Syringes with ½ unit markings and pens with at least ½ unit dosing increments should be used to facilitate more accurate insulin dosing when injecting small doses of insulin in multiple daily injection therapy. **E**
- Continuous glucose monitoring (CGM) is the recommended method of glucose monitoring. **C**
- If CGM is not available, 7 to 10 blood glucose checks per day with appropriate interpretation and action are usually needed to achieve target glycemia in this age group. **C**
- Lifestyle interventions, such as food choices and physical activity, designed to reduce the risk of subsequent cardiovascular disease in children with T1D, should already start in preschool age children and should be directed toward the entire family and not just the individual child with T1D. **C**
- Family-centered meal routines with restrictions on continuous eating habits (grazing) are important to ensure dietary quality and optimize glycemic control in preschool children. **C**
- Breastfeeding is recommended for all infants in accordance with WHO recommendations. This includes infants with diabetes. **E**
- Insulin dosing in breastfed infants can preferably follow a basal-bolus pattern with bolus dosing based on carbohydrate counting. **E**
- Diabetes education should be provided to staff at preschools and schools where children with T1D are enrolled, to promote equal and safely managed participation in all preschool/school activities. **E**
- Optimal glycemic control, minimizing exposure to both hypoglycemia and hyperglycemia will give the child the best opportunity to concentrate, participate, and learn while at preschool and school. **C**
- Weight, height (or length if <24 months), and Body Mass Index Standard Deviation Score (or percentiles) should be monitored at least every third month on growth charts in preschool children with T1D. **E**

3 | INTRODUCTION

This chapter focuses on components of care unique to toddlers and preschool-aged children with T1D. These guidelines are written for children with T1D aged 6 months to 6 years, but practical aspects might also be useful in younger children with insulin-treated diabetes. Children younger than 6 months of age at diagnosis should be investigated for other types of diabetes including monogenic diabetes, and their management is discussed further in ISPAD 2022 guidelines Chapter 4 on 'The diagnosis and management of monogenic diabetes in children and adolescents'.

Early onset T1D is associated with a high risk of early cardiovascular disease and premature death.[1] The strongest modifiable risk factor associated with diabetes-related mortality due to microvascular and macrovascular complications is HbA1c.[2,3] Glycemic target setting has been shown to positively affect outcomes.[4–6]

Preschool children are dependent on others for all aspects of their care. For the families (primarily parents) of preschool children with T1D, their diabetes teams and other caregivers (including school and daycare staff members and babysitters), treatment is a constant challenge. Despite the challenges, it is important to strive for normoglycemia, as current knowledge about the implications of dysglycemia makes reducing the likelihood of acute and chronic complications imperative from the time of diabetes onset.[7,8] Optimizing glycemic control for children in this age group often requires treatment strategies that differ from those employed for older children and adolescents with T1D. These strategies need to take into consideration the cognitive, motor, and social developmental levels of preschool children as well as their small body size and growth pattern.

In addition to their dependence on others (in this chapter referred to as "caregivers," i.e., parents) for insulin administration and glucose monitoring, preschool children are also dependent on others for aspects of their lifestyle related to healthy eating and physical activity. Lifestyle choices and preferences established during early childhood provide a window of opportunity for ingraining healthy habits that may be perpetuated throughout the child's life. The early establishment of positive behaviors may help to ameliorate the high risk of cardiovascular disease that is associated with diabetes. Providing adequate education and support for lifestyle changes requires that the multidisciplinary diabetes team uses a family-based approach to ensure that the whole family is appropriately supported to promote health.

Early childhood is an important time for establishing salutogenic[9] and adaptive health behaviors and parents and primary caregivers of young children play an important role in this process. Supporting caregivers while they become increasingly comfortable with intensive insulin treatment is vital, including support for the caregiver's own physical and emotional health.[10,11] It is also important to teach caregivers, strategies for helping their young child to become an active

participant in their own care. Young children can help caregivers complete diabetes-related tasks such as helping to select a finger for glucose monitoring, a site for injection/infusion, and selecting healthy foods. It is also recommended that caregivers employ think aloud strategies to begin to teach young children problem-solving skills.

Screening and promotion of optimal health-related quality of life should be regularly undertaken in preschool children with T1D as in any child with T1D.

Children younger than 7 years with T1D constitute a minority of the population of all pediatric patients with T1D. Small centers will have few very young patients and it will take longer to gain experience in the care of this patient group. Close collaboration between centers is necessary to optimize quality of care for preschool children with T1D.

4 | GROWTH AND DEVELOPMENT IN THE FIRST YEARS OF LIFE

For preschool children to experience normal growth and development, it is essential that they maintain near normoglycemia, aiming to maximize glucose time in target range, and are provided with sufficient nutrients. Restrictive diets or lack of food make it difficult to provide essential nutrients for growth and development and must be avoided. This requirement of sufficient nutrition is in part due to the brain's high metabolic requirement in infancy and childhood.

It is essential to monitor weight, height (or length if <24 months in accordance with national health care recommendations), and BMI-SDS (or percentiles) on growth charts in preschool children with T1D at least every third month. When telemedicine is used it is important to have access to valid data measured by health care professionals on height/length and weight at least every third month.

5 | THE BRAIN AND COGNITIVE DEVELOPMENT IN CHILDREN WITH EARLY ONSET T1D

Multiple risk factors have been associated with potential suboptimal cognitive and fine motor development in children and adolescents with T1D. These factors include early onset of disease (typically defined as <5 years of age),[12] disease duration, history of moderate to severe ketoacidosis (including those at diagnosis),[13] severe hypoglycemia (including seizures or unconsciousness)[14] and cumulative exposure to hyperglycemia.[15] A meta-analysis showed that the risk of cognitive disruption is largest for children with early-onset diabetes and the effect is detectable after a mean diabetes duration of 6 years. The mean effect size is moderate but might not be large enough to affect school performance.[8] Clinicians should be concerned about diabetic ketoacidosis (DKA), severe hypoglycemia and hyperglycemia all being detrimental for the health of the preschool child.[7]

During toddler and preschool years, the brain is highly sensitive to metabolic disturbances; potential abnormalities, particularly affecting white matter, have been identified in several neuroimaging studies of young brains exposed to glycemic extremes, as occurs in T1D.[16–18] The mechanisms by which early brain development is affected by T1D are not clearly understood. Long-term exposure to hyperglycemia as well as hypoglycemia (especially with seizures) and oxidative stress caused by glycemic variability are possible contributors. Both the duration and age of onset of diabetes appear to play a key role. For instance, metabolic conditions such as hyperglycemia and ketoacidosis at diagnosis may make the brain more vulnerable to subsequent metabolic insults.[7,8,19]

Existing meta-analyses report decrements in domains of intelligence quotient (IQ and verbal IQ in particular), executive function (attention, working memory, and response inhibition), delayed memory (episodic recall), and processing speed (paper-pencil) among children with T1D compared to age-matched children without diabetes, although these differences are generally not reported until the children are studied later in childhood.[12] It is possible that chronic exposure to different aspects of dysglycemia is additive, and that brain and cognitive changes only become apparent over time or that children need to achieve a threshold of cognitive maturity for differences to become measurable.[7]

Optimal glycemic control will give young children with T1D the best opportunity to concentrate, participate, and learn while at preschool and school. Health care professionals are best able to help children avoid any negative impact of T1D on everyday functioning by mitigating prolonged exposure to hyperglycemia, and by ensuring early identification and providing interventions for academic, cognitive, or motor issues. For further reading, the ISPAD 2022 guidelines Chapter 15 on Psychological care of children and adolescents with T1D comprehensively addresses this subject.

6 | GLYCEMIC TARGETS IN PRESCHOOL CHILDREN WITH TYPE 1 DIABETES

Optimizing glycemic control for preschool children with T1D is crucial for their future, both with respect to acute and long-term complications[2] as well as their neurocognition, brain structure,[7] and health-related quality of life (HRQoL).

ISPAD 2022 Consensus guidelines Chapter 8 on Glycemic Control Targets has recommended glycemic targets for hemoglobin A1c (HbA1c <7.0%, <53 mmol/mol). This target is applicable to all pediatric age groups and the aim is to optimize glycemia for each individual child. Children younger than 7 years with access to high quality diabetes care, including modern technology can achieve HbA1c 6.5% [48 mmol/L] or lower without a high risk of hypoglycemia.[20,21]

Optimizing glycemia is important in preschool age children diagnosed with T1D due to their higher risk of diabetes complications and premature death than persons diagnosed with diabetes later in life.[1] There is also evidence that hyperglycemia during childhood raises the risk of long-term complications even if substantial improvement is achieved later during young adulthood.[22] This evidence underscores the NICE guidelines, which encourage an HbA1c target ≤6.5% (≤48 mmol/mol)[23] and may fuel urgency within all guidelines to strive for HbA1c levels that are as low as safely achievable for preschool age children to reduce the risk of long-term complications of T1D. It is important that the diabetes team and family share the same glycemic targets; hence they should be set and evaluated together with the

child's family. Likewise, the glycemic targets need to be communicated to other caregivers (i.e., at preschool) to guide the child's treatment. From the onset, it is important for the entire diabetes team to communicate that near normoglycemia is achievable through diabetes education and clearly set glycemic targets.[4–6]

A CGM study in healthy children aged 2–8 years showed that glucose is in the range 4–7.8 mmol/L (72–140 mg/dL) 89% of the day.[24] A reasonable treatment goal after the initial remission period in insulin treated children younger than 7 years can be >50% of time in target (TIT) 3.9–7.8 (70–140 mg/dL) or >70% time in range (TIR) 3.9–10 mmol/L (70–180 mg/dL). Soon after diagnosis, during the remission period, a higher TIT or TIR is preferable.

It is important that both the diabetes team and families of young children use a language that tells the child that a glucose value can be high, low or in range, and that the glucose level is never "good" or "bad". The knowledge of a glucose value often calls for action, but never for blame or punishment. Rather than asking a child "*Your glucose is high—what did you do?*" or "*what did you eat?*," which can imply that the child has done something wrong, caregivers can be taught to "think out loud" and involve even young children in problem-solving (i.e., "*The glucose is high. What do we do when the glucose is high? Exercise and insulin can help. This time you will get insulin.*") This process can be started well before the child has an expressive verbal language, since the child's receptive language development starts early. This means that introducing diabetes related problem-solving gets integrated into the child's global development from diagnosis. It is important to be proactive when discussing glucose data and problem-solving in the clinic and to analyze positive examples together with the caregivers versus only reacting to glucose excursions.

7 | INSULIN THERAPY IN PRESCHOOL CHILDREN

Insulin treatment guidelines for preschool children are essentially similar to older children and adolescents, with age-dependent aspects taken into consideration. Insulin treatment always needs to be tailored for the individual child and planned together with their caregivers. Approval of insulin analogs for different age groups is regulated by authorities. See the ISPAD 2022 Consensus Practice Guidelines on Chapter 9 on Insulin treatment for further reading on insulin and insulin analogs in pediatric use. Worldwide, most preschool children with diabetes use insulin injections to manage their diabetes.

Insulin pumps offer both greater flexibility in insulin dosing and a better means to deliver very small, precise doses of insulin than injections and are thus considered the preferred method for insulin delivery in infants, toddlers, and preschoolers. A pump with high precision in delivering very small basal rates should be chosen for a preschool child. If pump therapy is not available or affordable, multiple daily injections (MDIs), with consideration of an injection port to reduce the number of injections, can be used.

When evaluating cost effectiveness and affordability of insulin pumps, psychosocial issues, such as quality of life and diabetes-specific emotional distress (both for the child and the caregivers) as well as metabolic aspects need to be considered.

Although insulin pump use is recommended, injection therapy is used in many centers for preschool children with T1D, especially in the following situations:

- when insulin pump treatment is not available or affordable.
- children who were using pumps have experienced pump failures or "skin reactions" that are difficult to adequately treat
- when the local diabetes team is inexperienced with using pumps in this age group. If so, advice should be sought from a more experienced center to provide the child with pump treatment and to optimize quality of care.

For safety reasons, all primary caregivers of very young children treated with an insulin pump need to be practically skilled in treatment with insulin injections in case of technical pump problems.

Pain and fear associated with insulin delivery can be reduced by behavioral strategies (i.e., distraction, deep breathing).[25] The usage of subcutaneous catheters such as Insuflon (Unomedical, Lejre, Denmark) or I-port (Medtronic MiniMed, Northbridge CA, USA) and changed every third day can be helpful.[26] Topical lidocaine can be administered before insertion of s.c. insulin ports for infusion or injections.

7.1 | Insulin dosing

Preschool children with optimal glycemic control usually need less insulin on a body weight basis than older children. The total insulin dose has been reported to be 0.4 to 0.8 U/kg/d (median 0.6 U/kg/d) in preschool children with well controlled T1D after the remission phase.[27] Preschool children have higher day-to-day variation in insulin needs than older children.[28] Insulin sensitivity varies with both age-appropriate activities and with age-appropriate napping. Preschool children may have higher insulin needs during day-time napping.

7.2 | Basal insulin

When using injections for insulin treatment, the unique diurnal pattern of insulin requirements in preschool children should be taken into consideration in designing an individualized basal dosing scheme.[29–32] The low insulin requirement and tendency toward low glucose levels are often most obvious during the night and especially between 3 and 6 AM. Preschool children often need much more insulin late in the evening between 9 PM and 12 AM and the overnight insulin needs are variable from night to night.[28] This creates typical patterns when designing basal insulin dosing plans. If basal analogs are used one should consider their action profile in relationship to insulin requirements.

The low body weight and thus low total insulin dose demands special consideration when using commercially available insulin pumps

and insulin preparations, especially in children with a body weight below 5–10 kg. Sometimes very small doses necessitate dilution of U-100 insulin, or an intermittent basal rate of 0 U/h for limited periods, i.e. every second hour during the night.[33,34] These approaches may help to meet the needs of the young child's insulin treatment and must be carefully discussed (with advantages and disadvantages) with the primary caregivers so that they are informed of the benefits and risks of the chosen strategy. Insulin should always be prescribed and documented in normal units to avoid hazardous misunderstandings regarding insulin dosing, especially if the child using diluted insulin is admitted to hospital. Any pump containing diluted insulin should be labeled with information regarding the currently contained concentration of insulin.

A glucose and meal-adjusted basal-bolus insulin regimen (delivered by injections or pump) requires that basal insulin delivery be fine-tuned by the caregivers in accordance with the child's current insulin sensitivity. Preschool children have a higher day-to-day variation in insulin needs than older children.[28] Insulin sensitivity can be increased after very active days, such as a days at the beach or in the snow, or after a day playing with friends. The overnight long-acting insulin or basal rate might then be reduced by 10% to 30%. Insulin sensitivity can be markedly reduced (increased insulin resistance), for example, during fever when the long- acting insulin or basal rate might need to be increased by 20% to 100% according to glucose levels. Under these circumstances, glucose levels must be carefully monitored and caregivers need constant (24 hour per day/365 days per year) access to support from the diabetes team.

7.3 | Bolus dosing

A glucose and meal-adjusted basal-bolus insulin regimen (delivered by injections or pump) can be adapted to the preschool child's daily activities and is the preferred type of insulin treatment. Twice daily insulin dosing in this age group does not give the flexibility needed to adapt doses to varying situations in daily life and requires a rigid pattern of eating to match insulin peaks, which is challenging in this age group and is associated with poor glycemic outcomes.[35,36] In settings with limited resources or when struggling with severe socioeconomic deprivation, including problems with insulin availability and administration, sometimes the only option is to give NPH insulin in the morning together with rapid-acting insulin at the time of the first meal of the day to provide some insulin for daytime meals. However, this regimen should be avoided if at all possible.

Preschool children often need proportionally larger bolus doses than older children, often constituting 60% to 80% of the total daily insulin dose (TDD). The often used rule of 500 (500/TDD = how many grams of carbohydrate [CHO] is covered by 1 U of insulin) for bolus calculations, as detailed in the ISPAD 2022 Consensus Guidelines Chapter 9 on Insulin treatment rarely fits the youngest children as it often underestimates the insulin dose.[37] One can use a 330 or 250 rule (gives 50%–100% more insulin) instead of 500. To evaluate and further tailor the child's insulin dosing it is necessary to repeatedly observe and calculate the correct proportion between insulin and CHO from real life meals.

The need for insulin at breakfast is often very high, and one might consider using 150/TDD in the calculation, and then evaluate and calculate from real life meals as above. At breakfast preschool children often have some degree of insulin resistance, and it is common to experience a marked glucose peak after breakfast despite an adequate insulin dose taken before the meal. For further reading, please see the ISPAD 2022 guidelines chapter 10 on Nutritional Management in Children and Adolescents with Diabetes. Increasing the insulin dose (lower insulin-to-CHO ratio) too much can risk hypoglycemia before lunch. In this situation, it may be helpful to give the prandial insulin 10 to 20 min before breakfast, lower the carbohydrate amount if it is high, and switch the carbohydrate type to a lower glycemic index (GI) carbohydrate. The need for a large bolus dose of insulin to cover breakfast might necessitate a very low basal rate during the following 3 hours.

The lower insulin requirement between 3 and 6 AM and higher insulin requirement between 9 PM and 12 midnight can affect the individual insulin sensitivity/correction factor for treating hyperglycemia. The usual 100/ TDD for mmol/l (or 1800 for mg/dL) often needs to be adjusted to give smaller correction doses during late night/early morning and larger doses in the evening.

Prandial bolus timing is important, regardless of mode of insulin delivery (pump or MDI). Pre-prandial bolus insulin given 15 min before the meal is preferable to insulin administered during or after the meal and should be routinely advised for all toddlers and preschoolers, even the most unpredictable eaters and when using formulations of insulin designed for faster uptake (faster aspart).[38] It is also important in hybrid-closed loop systems (see below).

Given the difficulties in anticipating carbohydrate intake in very young children, if needed the dose can be split with an insulin pump: a portion of the insulin dose is delivered before the meal and the remainder during the meal when eating is erratic or new foods are offered. Another possibility with a pump, is that a combination bolus (also called combo or dual wave bolus) can be used; that is, part of the bolus is given before the meal and the remainder over 20–40 min. If the child stops eating before the meal is finished, the remainder of the bolus can be canceled.

Small inaccuracies in calculation of up to 5–7 g CHO will usually not be problematic. Larger inaccuracies may result in hypoglycemia or hyperglycemia 2–3 h after eating, but not immediately. These can be anticipated and treated with additional CHO or a small correction dose of insulin at least 2 h after the meal.

When giving relatively large bolus doses, one must remember that they interact with the need for basal insulin in the following hours. Thus, the total basal rate can be relatively low, around 20%–40% of TDD. In preschool children, it is often estimated that the effect of a subcutaneous bolus of a rapid-acting insulin analog (lispro, aspart, or glulisine) lasts for only 2–3 h (active insulin time in pumps).[37]

When using MDIs with frequent glucose checks and meal-adjusted insulin dosing, one possible strategy is to give a rapid-acting insulin analog for all meals, except for the last meal of the day when

short-acting regular insulin can be used to ameliorate the increase in glucose before midnight. Part of the dose can be given as rapid-acting analog insulin, the insulins can be mixed in a syringe or given as separate injections (if an injection aid is used).

8 | PRACTICAL ASPECTS ON USE OF INSULIN PUMPS WITH AND WITHOUT CGM IN PRESCHOOL CHILDREN

Over the last few years pump size has decreased, pumps can deliver smaller doses, and CGM devices have become more accurate and more widely available making these therapies acceptable for preschool children. The safety of insulin pump and CGM use in this population appears to be similar to that seen in other age groups.

Yet, frequency of insulin pump and CGM use varies between centers.[39] Barriers to the use of these treatment options in pre-school children need to be explored and systems better adapted to this patient group.

For s.c. infusion of insulin in preschool children it is possible to use either flexible catheters or steel catheters. Both have advantages and disadvantages. Considerations include risk of pain, risk of kinking, number of adhesive points, insertion technique and skin reactions. The choice of infusion set needs to be re-evaluated during childhood as the child grows and subcutaneous fat distribution changes.

There are few data on special considerations regarding skin care in preschool children with T1D but CGM-related skin problems seem to be frequent in very young users.[40] In general, recommendations for site use (including site selection, site preparation, and site rotation) are similar as for older children. Many preschool children receive insulin injections and insert infusion sets and CGM sensors in their buttocks, an area often covered by a diaper. The abdomen, upper arm, and upper thigh are also commonly used. For children under the age of 6 years using insulin pumps, rates of scarring and lipohypertrophy are high but not different than in older children.[40]

8.1 | Hybrid closed loop with automated insulin delivery systems in preschool children with T1D

While hybrid closed loop insulin pumps (HCL) with automated insulin delivery (AID) are now relatively widely used in older children with T1D, during the past few years, their use in infants, toddlers and preschool children has largely been restricted to clinical trials.[28] Notably, the evidence from clinical trials suggests that HCL with AID can increase TIR, especially overnight, among very young children.[41] HCL with AID can reduce parental burden for managing diabetes-related care and reduce perceptions of parenting stress.[42,43] Making certified systems with this technology available for children younger than 7 years, tailoring the algorithms to the age-specific needs of this patient group, and further developing clinical and research experience using this treatment modality in preschool children will be important. Age-specific challenges to address in automated systems include the small insulin doses needed, often well below 10 U per day,[44] the large differences in physiological insulin needs during different parts of the day, significant day-to-day variation in insulin needs, and safety concerns to avoid accidental insulin dosing.

When first implementing HCL-systems there may be a need for some "re-learning" among diabetes teams and caregivers of young children. They should avoid late bolus dosing for carbohydrates, which on an automated system results in "basal" increases by the algorithm when the glucose is rising without adequate insulin on board. A subsequent late bolus to cover the carbohydrate intake combined with the "basal" increase may precipitate hypoglycemia. Additionally, if basal insulin is suspended due to impending hypoglycemia, the amount of carbohydrate needed to treat hypoglycemia may be less than is usually required with standard pump therapy. The need to trust the system's capacity to correct glycemic excursions is a new challenge for caregivers.

With some diabetes centers employing advanced technologies for patients from the time of diagnosis, healthcare providers now sometimes encounter families of young children with T1D who have never experienced any other mode of insulin treatment. Nonetheless, for safety reasons, all families need to be equipped, experienced and skilled in insulin injections and capillary glucose monitoring ("finger-prick") in case of technical problems with the devices or algorithms.

9 | PRACTICAL ASPECTS ON USE OF MULTIPLE DAILY INSULIN INJECTIONS IN PRESCHOOL CHILDREN

When an insulin pump is not affordable or available, MDI is a treatment that can be used safely and effectively.

High precision insulin dosing adjusted by carbohydrate counting is difficult when using insulin pens or syringes filled with insulin U-100. Syringes with ½ unit markings and pens with at least ½ unit dosing increments should be used. Diluting insulin to 10 U/ml increases the possibility to dose in small steps and to adjust insulin dosing to anticipated carbohydrate intake and current glucose levels.

Giving insulin pre-meal is also necessary when insulin is administered via injections. Giving all the insulin in one injection necessitates a skilled caregiver estimation of the child's anticipated eating. This can be achieved by encouraging eating practices that make it easier to predict intake (see Nutrition section below).

An individually programmed bolus calculator (i.e., a phone app or a paper-and-pen scheme) can simplify calculation of bolus doses.

It is important to create a calm situation when injecting insulin. Insulin can be injected in the buttocks with the child sitting face-to-face on the lap of a caregiver. Some children need to see what is happening and injecting in the abdominal region can make this possible. Upper arms and legs can also be used for injection but may risk the child moving their limb and require the caregiver to hold the child, creating an unpleasant injection experience.

The major challenge for many caregivers of toddlers and preschoolers on MDI is how to handle the complicated situation of more

or less simultaneously cooking, calculating the insulin dose, injecting the child and then transferring focus to eating together with the family. Cooperation between two caregivers is often a necessity in this complex situation.

10 | GLUCOSE MONITORING

In this chapter, blood glucose (SMBG) values refer to glucose values measured by capillary blood check ("finger prick" and "blood glucose monitoring") although meters generally display plasma glucose concentrations. Since plasma glucose is 11% higher than whole blood glucose, this term is used when exact numbers are mentioned. The term "glucose value" refers to a glucose value from either continuous glucose monitoring (CGM) or a capillary blood check. The use of CGM (rtCGM or isCGM) is recommended in all insulin treated children younger than 7 years.

10.1 | Blood glucose checking

Families should be taught how to measure and interpret capillary blood glucose values (SMBG). The limited capacity of the preschool child to verbally communicate necessary information related to self-care increases the need for high quality and frequency of glucose monitoring. It is important for the preschool child that the caregivers can perform the monitoring in a way that gives the child a sense of security and trust. Accuracy in everyday monitoring situations should be ensured by follow up with the diabetes team. The child should be introduced to glucose monitoring and interpretation according to age appropriate and individual capabilities, as the development of the mathematical understanding of numbers and time is gradual.

While independent self-care can never be expected from any preschool child with T1D, most typically-developing children with diabetes can perform blood glucose checks and perform some basic interpretation by age 7 years. However, this should always be overseen by a caregiver.

General advice on SMBG monitoring is available in the ISPAD guidelines on Glucose monitoring. In children younger than 7 years-old, the recommended checking frequency of 4–6 times per day is rarely sufficient to achieve target glucose and HbA1c levels. A high proportion of time is spent out of glycemic target range.[45] Even with a higher monitoring frequency of 7 or 10 checks per day, undetected hypoglycemia and hyperglycemic events in insulin treated preschool children are common.[46]

Nighttime SMBG is recommended by many diabetes teams and performed by many families with pre-school children with T1D.[47] Preschool children with diabetes can spend a long time in the hypoglycemic range without detection,[36,48] despite nighttime monitoring of SMBG.[46] The normal activities of the child must be interrupted to measure a blood glucose value during daytime.

Thus, relying on SMBG as the only way of monitoring glucose has several limitations but is a necessary tool to master for all caregivers of a preschool child with T1D.

10.2 | Continuous glucose monitoring

CGM provides an effective mode of monitoring for low and high glucose levels. Qualitative reports from caregivers suggest CGM can promote a sense of safety, decreased worry, and greater comfort with other caregivers when used as part of remote monitoring.[49] When available and affordable, CGM should be used as a tool for adjusting insulin doses. With use of newer systems, real-time CGM use is high and sustained in young children with T1D and significantly reduces hypoglycemia.[50] Reduced glycemic variability was observed in real world use of CGM among a multinational cohort of young children.[51] Health care providers should counsel caregivers on how to reduce CGM-related challenges, which can include pain from insertion, disruptive alarms, limited areas to place a sensor, skin and adhesive problems, and data overload. Health care providers fill an important role in educating families of young children about diabetes technologies, including CGM, and need to help families to establish realistic expectations of the benefits and challenges of CGM use.[52]

The ability of some CGM devices to remotely transmit glucose values to a phone can be of benefit for caregivers who rely on others for care of their child, for example, while at day care or preschool.[53]

11 | NUTRITIONAL NEEDS OF THE PRESCHOOL CHILD WITH T1D

Optimal nutrition is required to provide sufficient energy and nutrients to meet the rapidly changing needs of children at this stage of life. Relative to their body weight, children's nutrient and energy requirements are greater up to around 4–5 years of age, after which their growth rate slows and their nutrient needs decrease relative to their body size.[54]

Breastfeeding should be encouraged for all infants,[55] including infants with diabetes. Complementary foods, preferably iron-rich, should be introduced from 4 to around 6 months of age. If breastfeeding is not possible, an iron-fortified infant formula should be given as the main milk drink until 12 months of age.

A routine regarding breast- or formula-feeding is important for infants with diabetes as this enables appropriate interpretation of glucose levels and basal and bolus insulin adjustments. This may involve 3–4 hourly feeds (of approximately 150–240 ml) during the day with complementary solids. Continuous or hourly breastfeeding is discouraged as this makes insulin dosing difficult while bolusing every third to fourth hour during day-time works practically. Breast milk has approximately 7.4 g CHO per 100 ml, so for infants 6 months and older it is possible to bolus before the feed for at least 5–7 g CHO and 15 g CHO in older babies (>9 months).

Dietary recommendations are based on healthy eating principles suitable for all preschool children, with the aim of establishing family-based meal-time routines that promote glycemic control and reduce cardiovascular risk factors. Carbohydrate counting is important to permit the matching of insulin dose to carbohydrate intake on intensive insulin regimens and should be taught to the family at the onset of

diabetes (See nutrition chapter 10). Nutritional advice must be individualized and adapted to cultural and family traditions.

A pediatric diabetes dietitian should provide education, monitoring, and support at regular intervals throughout the preschool years, as caregivers of preschool children with diabetes report meal-times as one of the most difficult components of their child's care.[56] Preschoolers require more frequent dietetic review than older children, with a suggestion for reassessment at least twice annually until the age of 6 years (See ISPAD 2022 Consensus Guidelines Chapter 10 on Nutritional Management in in Children and Adolescents with Diabetes). It is important to provide caregivers guidance for appropriate food quantities for age, including minimum and maximum carbohydrate amounts, particularly as food intake may drop off during the second year of life and following weight regain after a T1D diagnosis.[20]

There is international agreement that carbohydrate should not be restricted in children with T1D as it may result in deleterious effects on growth and brain development.[57,58] Care should be taken when giving dietary education, so that methods of quantifying carbohydrates do not increase saturated or trans-fat intake. Although caregivers may prefer high- fat snacks to avoid affecting glucose levels, this should be discouraged as they will provide unnecessary calories, an unhealthy fat intake, and negatively impact dietary quality. Studies suggest that consistency in children's intake[59] and balanced meals containing protein, fat and carbohydrate[60] may be helpful methods for reducing post-prandial glycemic variation.

Preschool children with T1D should consume a diet that emphasizes vegetables, fruit, whole grain bread and cereals, dairy foods and appropriate types and amounts of fats. Low fat diets are not suitable for children under 2 years of age. Lower glycemic index (GI) choices, can be introduced as substitutes for higher GI food choices. Iron deficiency can be a concern in this age group; adequate consumption of lean meat or alternatives is important and should not be overlooked because of the increased focus on carbohydrate.

A *guide* to the macronutrient distribution of the total daily energy intake in preschool children is shown below. However, this should be based on an individualized assessment and with respect to the family's eating pattern prior to the child's diabetes diagnosis and day-to-day variations in the child's appetite.

Carbohydrates: 40–50 Energy (E) %. Average intakes 110–140 g/d in children aged – 5 years; 200 g/d in children 6 to 10 years.[57]

Protein: 15–20 E % (decreasing with age from approximately 1.5 g/kg body weight/day in 6-month-old infants to 1 g/kg body weight/day in preschoolers).

Fat: 30–35 E % (less than 10 E% saturated fat, less than 10 E% polyunsaturated fat, and more than 10 E% mono-unsaturated fat). Infants less than 12 months may consume up to 40% energy from fat.

Fruit and vegetable intake remain of particular concern and ways to incorporate these into the whole family's diet, including the preschool child's, should be discussed.[59,61] Examples of recommendations from Australia, United States, and the Nordic countries are expressed in different ways but consistent in content: 180 g vegetables (2½ servings) and 150 g fruit (1 serving) daily from 2 years of age; or 1½ serving of fruit and vegetables daily between 1 and 3 years. 400 g of fruits/vegetables are recommended each day from 4 years of age.

The dietary quality of preschool children with diabetes is similar to or poorer than their peers without diabetes.[62] Preschool children with T1D consume less fruit and vegetables and have higher saturated fat intakes than peers[63] and then recommendations would advise.[64,65] This may increase the risk of future cardiovascular disease. Eating habits in young children influence food choices later in life,[66] so early intervention with increased attention to an increase in fruit and vegetable intake and decrease in saturated fat is needed. It is helpful to counsel caregivers that young children with or without diabetes may require up to 10 exposures to a new food before it is accepted[67] and to educate caregivers on how to make appropriate adjustments to pre-prandial insulin dosing or meal planning (e.g., pairing a new food with a familiar food) to avoid dosing during or after the meal. It can also be helpful to remind caregivers that miscalculations of carbohydrate content <5 g rarely affects the postprandial glucose levels.

More children with T1D have an overweight body mass index compared to children in the general population,[21,64,68,69] and this is most pronounced in the youngest children (<6 years).[70,71] It is important to plot the growth chart including assessments of weight for length or height at least at 3-month intervals to identify excessive weight gain, in order to commence interventions that involve the whole family. Diabetes associated risks of extra caloric intake as over-treatment of hypoglycemia or excessive feeding before bed because of parental fear of hypoglycemia need to be explored if the child develops overweight/obesity. Encouraging participation in family meals has been recommended to promote dietary quality and social interaction.

Age-appropriate finger foods should be encouraged for self-feeding, and the reintroduction of a bottle as an easy method of carbohydrate intake discouraged. Bottles can lead to overconsumption of fluids, increasing carbohydrate intake and placing other nutrients at risk.

12 | ESTABLISHING POSITIVE FOOD BEHAVIORS AND MEAL-TIME ROUTINES

Establishing positive food behaviors and meal-time routines are important for preschool children with T1D, as these behaviors impact glycemic control[56,72] and set the stage for life-long appropriate nutrition practices.[66] It is important that caregivers model eating practices and the preschool child is exposed to new foods in the context of family meals. Early childhood developmental traits, including seeking independence, transient food preferences, variable appetite, food refusal, and behavioral resistance often make mealtimes challenging for caregivers of children with diabetes. Caregivers of children with T1D report more disruptive meal behaviors, including longer meal duration and more frequent food refusal compared with controls[69,73,74]; even for children using insulin pumps.[75] Research has

demonstrated positive correlations between suboptimal dietary adherence and higher glucose levels.[56,63,75,76] Caregivers' fear of hypoglycemia associated with food refusal or unpredictable dietary patterns can result in force feeding, grazing continually over the day, and postprandial insulin administration, causing prolonged periods of hyperglycemia.

To assist the reliable intake of carbohydrate at mealtimes and to minimize food refusal, the following strategies should be offered:

- structured mealtimes
- avoidance of continuous eating habits as this has been associated with poorer glycemic outcomes in young children[59]
- small snacks including limits on low carbohydrate foods as these fill the child up
- limits on the time spent at the table; for small children, mealtimes should be limited to approximately 20 minutes per meal.[77]
- avoidance of force feeding
- team members should reassure caregivers that hypoglycemic episodes related to inadequate carbohydrate consumption are usually mild.

Caregivers should be advised that postprandial bolus insulin can become an established habit and reinforce anxiety about the child under-eating. Fear of hypoglycemia can lead to under-bolusing for meals, resulting in inadequate bolus doses given over the day and subsequent hyperglycemia. Continuous eating (grazing) makes interpretation of glucose levels and insulin dose adjustments difficult. A regular meal pattern with one small snacking episode between meals (7–15 g carbohydrate preceded by an appropriate insulin dose) may reduce food refusal as the child may be hungrier at main meals. Unreasonable expectations of a child's intake may result in food refusal and subsequent hypoglycemia. Food refusal should generally be dealt with effectively and similarly to toddlers without diabetes. It is important to emphasize parental patience and to encourage caregivers not to use food bribes.

All diabetes team members should provide the family with clear and consistent messages regarding food and mealtime behaviors.[78] Distractions such as the television and toys should be removed at mealtimes.[65] Research has demonstrated that disruptive child behaviors can be reduced by establishing specific rules and consequences for mealtimes and teaching caregivers behavioral strategies for meals.[79] Stepwise, the child needs to establish an age-appropriate positive connection between insulin, food and health (i.e., "*I get insulin, I eat and thus I can jump this high and feel great*").

13 | LIFESTYLE FACTORS IN PRESCHOOL CHILDREN

The American Heart Association (AHA) has identified that T1D is associated with extremely high risk of cardiovascular disease, calling for treatments to minimize this risk.[80] Lifestyle habits, such as nutritional preferences,[66] physical activity,[81] and time spent sedentary,[82] that are established in childhood often persist into adulthood. Thus, lifestyle factors in early childhood have a dual impact on later cardiovascular risk, observable both as early markers of atherosclerosis during adolescence[83] and as a set of behaviors that influence the child's risk of cardiovascular disease as an adult and even into senescence.

Children tend to follow the lifestyle habits of their caregivers and entire family regarding physical activity,[84] TV watching[85] and food choices[61,86,87] in childhood and then subsequently throughout their adult lives.[66] Lifestyle supporting interventions should thus be directed toward the caregivers and entire family and not the individual child with T1D.

13.1 | Physical activity

Physical activity and sleep confer many health benefits for all children. Physical activity has a strong, graded, inverse cross-sectional relationship to insulin resistance[88,89] and body fat.[90] High-intensity physical activity is the most effective type of activity to reduce cardiovascular risk.[91] Engaging in regular physical activity is also necessary to acquire and improve gross motor skills.[92] Many countries recommend at least 60 min/day of moderate and vigorous physical activity for all children,[93] and WHO recommends this at least from 5 years of age.[94]

Preschool-age children engage in patterns of physical activity that are different from older children and characterized by multiple small bursts of activity.[95] This difference can complicate how to quantify the physical activity of a preschooler. Asking caregivers about how, where, and how often (vs. how long) their preschooler plays may be a way to help quantify their physical activity.

General facilitators of physical activity for preschoolers include access to safe play environments and organized activities, their own preference for being physically active, positive parent modeling of physical activity, spending time outdoor and peer interaction.[96,97]

Data suggest that both having diabetes and being a girl represent risk factors for greater physical inactivity in preschool-age children.[98]

13.2 | Sleep

Sufficient and high-quality sleep plays an important role in overall health and may also be associated with hyperglycemia and glycemic variability in children with T1D.[99,100] The American Academy of Sleep Medicine recommends infants sleep between 12 and 16 h per day, toddlers sleep between 11 and 14 h per day, and preschoolers sleep between 10 and 13 h per day including naps.[101,102] However, recent studies in young children with T1D report much shorter than average sleep durations (8 h per night) based on parent-report and actigraphy.[100,103] Both children and caregivers experience sleep disruptions and restriction because of nighttime caregiving and caregivers commonly report fear of nighttime hypoglycemia.[11,104,105] Infants and toddlers sleeping pattern during the day needs to be taken into consideration when programming the insulin pump. There is emerging evidence suggesting automated insulin delivery systems can reduce

the number of parental awakenings and fear during the night and improve parental perceptions of sleep quality.[42]

14 | KETONE MONITORING

Ketoacidosis is a life-threatening acute complication of diabetes. Six percent of children younger than 6 years in the United States and 4% of children in Germany/Austria (data from the T1D Exchange clinic registry and the Prospective Diabetes Follow-up Registry: DPV) have suffered from ketoacidosis during the past year.[106] Education of families on prevention of ketoacidosis is an essential part of diabetes care, especially as young children are physiologically prone to develop ketosis. See the ISPAD Guidelines on Diabetic Ketoacidosis chapter 13 for further advice.

The high incidence of gastroenteritis with vomiting and risk of misinterpreting vomiting due to insulinopenia makes monitoring of ketones important in this age group. Measuring ketone bodies in blood (betahydroxybutyrate, BOHB) should be the primary method of detecting and monitoring ketosis in preschool children with T1D; see the ISPAD Guidelines chapter 12 on Sick days. Blood ketone checking gives the caregivers and health care professionals timely information regarding ketone levels and their rise or fall to provide advice over the phone or in the emergency room.

Ketones should be monitored when there is a suspicion of lack of insulin raised either by high blood glucose (2 values above 14 mmol/L [252 mg/dL] within 2 h that do not decline with an extra insulin dose) or when the child shows symptoms suggestive of ketosis (vomiting, nausea, abdominal pain or unclear illness). It is important to educate and remind caregivers of young children that insulin always should be given by s.c. injection (with a syringe or a pen) when treating ketonemia (without DKA) even if the child usually is treated with an insulin pump. See the ISPAD Guidelines chapter 12 on Sick days for further advice on treatment.

Measurement of acetoacetate in urine with a dipstick can be used as an alternative to blood ketone measurement but gives different information. As preschool children do not urinate on command, results from blood ketone monitoring will be more easily available for the caregiver parent unless the child uses diapers. Cotton balls can be put in the diaper to absorb urine which can then be applied to the dipstick.

15 | HYPOGLYCEMIA

Hypoglycemia, including caregiver fear of hypoglycemia, is a limitation to striving for normoglycemia in preschool children, see ISPAD guidelines chapter 12 on hypoglycaemia.[47,105,107] Young age has traditionally been regarded as a marker of high risk of severe hypoglycemia during insulin treatment. Inherent in this risk, is the observation that preschoolers are erratic in their daily life (food intake, activity levels, sleep, and sick days) predisposing to hypoglycemia. Many preschool children are also unable to identify and articulate their symptoms, making it very difficult for caregivers to detect these symptoms. There is an additional risk due to prolonged nocturnal hypoglycemia, common in children younger than 7 years with T1D.[46,108–110] HCL studies indicate that preschool children have a high day-to-day variation in insulin need,[28] which may also contribute to risk.

Data suggest the frequency of severe hypoglycemia has decreased over time in all children with T1D and that there is no longer a clear association between lower HbA1c and higher risk of hypoglycemia.[111,112] Moreover, specific to preschoolers, Germany and Austria (DPV), USA (T1DX)[106] and Sweden all report that no more than 3% of children younger than 6 or 7 years with T1D have experienced a severe hypoglycemic event with seizures/unconsciousness during the previous year.[21] These data suggest the use of insulin pumps, hybrid closed loop systems, insulin pumps with a suspend before low algorithm can reduce the time spent in hypoglycemia. Access to CGM and predictive alarms for upcoming hypoglycemia appear to increase the probability of early detection and prevention of hypoglycemia.

These technologies represent an opportunity to turn the corner in reducing the risk of severe hypoglycemia in preschool-age children with T1D. Caregivers who lack the knowledge or confidence to use these technologies effectively in their child's daily management may benefit from advanced diabetes education to understand glucose patterns and how to use alerts on their child's CGM to recognize and treat potentially dangerous glucose trajectories (e.g., rate of glucose decrease shown by arrows pointing downward).

The fear of a hypoglycemic event, rather than the frequency of hypoglycemic events, is associated with higher HbA1c and lower HRQoL,[107,113] suggesting the role of fear cannot be underestimated for caregivers of young children with T1D. Fear of nocturnal hypoglycemia is a particular challenge. Emerging evidence supports that behavioral interventions may reduce caregivers fear and there is evidence that consistent CGM use can reduce time in hypoglycemia in young children.[50,114] Asking in a clinic visit about typical frequency and severity of hypoglycemia is encouraged. It may also be helpful to use validated surveys that ask about thoughts and feelings during and after the hypoglycemic event to identify caregivers who might benefit from treatment.

15.1 | Treatment of mild hypoglycemia in infants and preschool children

Oral glucose as tablets, gel, or a drink is the preferred method of hypoglycemia treatment. The dose of glucose should be easily accepted and quickly ingested by the child. The recommended dose (0.3 g glucose/kg bodyweight) will raise plasma glucose approximately 2.5–3.6 mmol/L (45–64 mg/dL) (guidelines chapter 12 on hypoglycemia).[115] In young children 5–7 g carbohydrate is usually adequate, and it is important not to give too much carbohydrate when treating hypoglycemia to avoid subsequent hyperglycemia. This risk is high in young children with a small body size.

To treat hypoglycemia in breast- or formula-fed infants, carbohydrate gel, diluted juice, or a glucose polymer from a spoon or bottle

can be offered. Honey should not be given to infants younger than 1 year due to risk of botulism.

Giving something that contains fat (i.e., milk and chocolate) will slow gastric emptying and cause a slower rise in plasma glucose.[116] Sucrose sweetened confectionary should not be routinely used to treat hypoglycemia, as it can lead to increased risk of dental caries.

16 | CARE OF THE NEWLY DIAGNOSED INFANT, TODDLER, OR PRESCHOOLER WITH DIABETES

The care of the newly diagnosed child with T1D is a key opportunity for successful diabetes treatment. The diabetes team needs to have clear routines regarding treatment initiation for newly diagnosed infants, toddlers and preschool children with diabetes and be ready to tailor these further to fit the individual child and family.

Preschool children, especially toddlers, have a high risk of rapidly developing ketoacidosis at diabetes onset. Early detection and fast referral to a hospital with competence in management of DKA in very young children is lifesaving. Please see ISPAD 2022 guidelines Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State.

After DKA has resolved, or directly following diagnosis, if DKA is avoided, the immediate treatment goal should be to restore and maintain normoglycemia.

Carbohydrate counting, meal-time routines and nutrition need to be taught and discussed during the first days with insulin treatment. The education needs to be tailored to the individual family's crisis reaction upon diagnosis and preexisting understanding. The education needs to be given in a culturally sensitive manner and with a high respect of parental integrity.

Very young children with T1D may benefit from introduction of an insulin pump and CGM at or soon after diagnosis. Both devices can offer families greater ability to fine-tune insulin delivery when navigating the partial remission period.[117–120]

The professional diabetes team needs to get acquainted with the family's structure, habits and beliefs regarding lifestyle and upbringing of young children to develop individualized diabetes care plans that promote optimal habits and insulin treatment routines or can inform a rationale for habits that need to be changed.

The diabetes team should have programs and resources available to promote caregivers resilience and long-term capacity to provide developmentally appropriate levels of daily diabetes management as the child grows.

17 | LIVING WITH DIABETES IN THE FAMILY

For people living with T1D and their families, the management of the disease is complex and individual. Daily challenges imposed by T1D include cognitive and emotional burdens that can take the form of increased vigilance to dietary intake, symptom monitoring, and frustrations with glucose excursions. For caregivers of preschool children with T1D, additional complexities are encountered, including the necessity to adapt to developmental changes to ensure adequate psychological adjustments for the child and themselves, and to facilitate care in the context of other care providers such as preschool staff. Clinicians need to be aware of the overwhelming sense of responsibility and worry which parents of preschool children with T1D can feel.[121] Caregivers who have access to a supportive network (relatives and/or friends) have lower risk of diabetes-related stress and burnout.[10] It is important to educate secondary caregivers about T1D and insulin treatment. Attention should be given to the needs of the siblings of a young child with T1D.

As children grow up, they understand more about health and illness. When appropriate, it needs to be explained that diabetes is not caused by eating too much sugar, and that you cannot catch diabetes from another person. This needs to be intentionally taught to friends and relatives to avoid common misconceptions about diabetes.

Caregivers are an integral part of the diabetes team and have the most important supportive role to play over the years as their children eventually learn to self-manage their diabetes. Providing this support can be difficult when caregivers have their own stressors to deal with, and struggle with the constant vigilance needed to ensure the safety of their child. During young childhood, caregivers take responsibility for all diabetes-related tasks. It is important that they do this in a way that is neither threatening nor frightening for their child. Involving the child in aspects of diabetes management as soon as possible (e.g., using think aloud strategies when performing diabetes management, incorporating choice options when appropriate "What side of your bottom for your pump site? Pick one or I will") is recommended, so the child can begin to develop a sense of ownership/management of their own health. A supportive and emotionally warm parenting style is important for promoting improved quality of life for children with T1D.

Establishing good habits in the early years may form the basis for optimal life-long diabetes self-management. The way that caregivers model diabetes-related tasks will have a direct impact on the way their children learn. Supporting caregivers toward a positive adjustment to living with diabetes will help them to effectively model those tasks and assignments involved in daily life with diabetes as preschool children learn from examples.

It is important to engage all primary caregivers in diabetes care from the onset, and to keep them involved in everyday diabetes care throughout the childhood years and to avoid that responsibility for diabetes self-care is carried by only one primary caregiver.

18 | SCREENING CHILDREN FOR PSYCHOSOCIAL DISTRESS

Regular screening of children for psychosocial distress is important to ensure that difficulties are identified early, and appropriate support and treatment plans established as soon as possible. Most children are

not able to complete questionnaires or report on their own level of emotional distress in a reliable manner until they are approximately 7–8 years of age. Therefore, both talking with them directly about how they feel, and asking their caregivers to report on their children's psychosocial well-being is recommended. Including the child in the discussion is important and asking the child direct questions is essential. *What do you do for your diabetes that you are proud of? What parts of diabetes are easy for you? What parts of diabetes are annoying for you? Who are your biggest helpers in caring for your diabetes? If you could change something about your diabetes, what would it be?*

Members of diabetes teams need to develop clinical skills in talking directly with the very young child. This is sometimes a time consuming but necessary task.

Repeated meetings together with the child and caregivers are often needed to establish and continue an ongoing dialogue with the very young child. Telemedicine can contribute new challenges in caring for the preschool-age child (e.g., very young children may be shy or become distracted by the telemedicine equipment/setting). Therefore, when using video-based telemedicine with families, it may be necessary for diabetes teams to allot additional time to re-establish rapport with the child. Some strategies to try may include normalizing the telemedicine experience by asking the child to share a treasured item (e.g., toy or game) or to introduce the practitioner to their pet and to encourage interaction between the caregiver and child.

There are several pediatric measures of depressive symptoms that are validated and reliable for use with children as young as 7 years of age, varying in length and depth of detail.

Parental anxiety and fears can have a direct and negative effect on diabetes management and health outcomes. It can be associated with depression; however, these are two separate conditions and should be treated separately. They can have an opposite effect on diabetes management and control, supporting the recommendation to assess them separately.

19 | PRESCHOOL CARE

Legislation protects children with T1D in many countries. Schools must make reasonable adjustments to ensure that children with disabilities are not put at a substantial disadvantage compared with their peers. For diabetes, this means that preschools should have enough staff trained to allow the child with diabetes to take part in all aspects of preschool and school life without loss of quality in insulin treatment. Contingency plans must be in place to quickly train replacement staff.

In addition to ensuring the rights of the child with diabetes, it is important to create trust and cooperation between the preschool, the family, and the diabetes team. An individual diabetes management plan is needed in this collaboration and should include information about and practical training in the use of diabetes-related technologies. The child's young age and limited capacity to verbally discuss aspects of self-care need to be offset by well trained staff, written plans and an ongoing dialogue with the primary caregivers. Both the caregivers and the diabetes team need to share the responsibility for educating the preschool institution, especially when the child is newly diagnosed with diabetes or when an additional diagnosis such as celiac disease occurs. Working with the preschool staff on carbohydrate counting enables the appropriate doses of insulin to be given in relation to the food intake and glucose levels.

In countries where there are no regulations to support the child with diabetes, the diabetes team together with the parent organizations should advocate for improved regulations.

20 | CARE FOR THE PRESCHOOL CHILD WITH T1D IN LIMITED RESOURCES SETTINGS

Whenever possible, the guidelines described in the preceding sections should be followed. Treatment strategies and targets (such as HbA1c) need to be individualized and adapted to local circumstances.

Treatment of preschool children with T1D in contexts with generally high under-5 mortality-rates is an extreme challenge. Adding diabetes to general threats to health and survival such as infectious diseases and accidents puts the child in a hazardous position. Young children have a high risk of life-threatening ketoacidosis, which can be misinterpreted as gastroenteritis unless a high level of awareness and monitoring capabilities are available.

If possible, priority should be given to the youngest patients to get best possible access to monitoring of glucose and ketones. Flexible insulin regimens are preferred as the insulin needs of the young child is variable from day-to-day.

Breast-feeding should be recommended for children with diabetes on the same basis as other children in accordance with local traditions and recommendations. Preschool children with diabetes should follow the same guidelines for vaccination as healthy peers. Monitoring of weight and height/length is essential.

For further advice see the ISPAD Guidelines chapter 25 on limited resources.

21 | FUTURE NEEDS OF PRESCHOOL CHILDREN WITH T1D

"Diabetes during early childhood creates a psychosocial challenge to the families of these children. Successful management of infants and toddlers with diabetes depends on a well-functioning and educated family, the availability of a diabetes health care team experienced in the treatment of these youngsters, and the involvement of the extended family, child care personnel and others who play a role in their daily care."[122]

Children younger than 7 years with T1D constitute only approximately 10% of the population of all children (below 18 years) with T1D, but in many countries the incidence in this subgroup is increasing.[123] Collaboration among centers is thus necessary to conduct pathophysiological, epidemiological and clinical studies regarding

treatment strategies and tools (both technical equipment and pharmacological) and outcomes studies in this age group that are sufficiently powered. Moreover, when the youngest children with T1D are included in these studies, data regarding children with early onset diabetes must be presented separately to enable subgroup analysis.

The addition of new tools should enable families living with T1D to provide increasingly effective therapy and support for preschool children with diabetes. There is a need for effectiveness and implementation trials of the newer diabetes technologies in preschool-age children (e.g., HCL/AID) to expand on the outcomes of current smaller RCT/clinical trials. Access to this kind of equipment must be made available for young children with diabetes and not restricted only to older persons.

Evidence-based family interventions to improve both metabolic and psychosocial outcomes in both the short- and long-term need to be developed. There is also a need for additional research and interventions targeting lifestyle behaviors and diabetes in preschool-age children (e.g., sleep, physical activity, and diet/nutrition).

AUTHOR CONTRIBUTION

All authors contributed to all parts of the writing process and are equally responsible for the text.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13427.

DATA AVAILABILITY STATEMENT

NA. This chapter is a clinical consensus guideline based on published references and clinical expertise.

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How to cite this article: Sundberg F, deBeaufort C, Krogvold L, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Managing diabetes in preschoolers. *Pediatr Diabetes*. 2022;23(8):1496-1511. doi:10.1111/pedi.13427

Received: 24 October 2022 | Accepted: 27 October 2022

DOI: 10.1111/pedi.13447

ISPAD GUIDELINES

ISPAD WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Ramadan and other religious fasting by young people with diabetes

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Funding information
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KEYWORDS: fasting, Ramadan, religious fasting, type 1 diabetes

1 | WHAT IS NEW OR DIFFERENT

- The 2022 edition of the guideline provides updates of previous sections and includes fasting in other religions in addition to Ramadan.
- Evidence on the use of continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) during fasting.
- Fasting in young people with type 2 diabetes (T2D).

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | Pre-fasting counseling

- Pre-fasting counseling and diabetes education is recommended for all children and adolescents with type 1 (T1D) and T2D who want to fast for religious reasons. **E**

- Pre-fasting education addresses insulin type and action, glucose monitoring, nutrition, physical activity, sick days, hyperglycemia, as well as recognition and treatment of hypoglycemia. **E**
- Pre-fasting counseling on the permissibility and necessity of finger prick self-monitoring of blood glucose (SMBG) or insulin injection during fasting to prevent acute complications is important. **E**
- Optimizing glycemia before fasting is an essential measure to ensure safe fasting. **C**
- The presence of hypoglycemia unawareness needs to be excluded pre-fasting and monitored during fasting. **C**

2.2 | Glucose monitoring

- Frequent SMBG or CGM is recommended during fasting to minimize the risk of hypoglycemia and detect periods of hyperglycemia. **B**
- Use of real-time CGM (CGM) or intermittently-scanned CGM (isCGM) may facilitate the adjustments of insulin dosing during fasting. **E**

2.3 | Nutritional management

- Consider the quality and quantity of food offered after breaking the fast to prevent acute complications, excessive weight gain, and adverse changes in lipid profile. **C**
- Consider meals based on low glycemic index carbohydrates and include fruit, vegetables, and lean proteins. Monounsaturated and polyunsaturated fats should be used instead of saturated fats. Sweets and fried foods should be limited, and sweetened drinks avoided. **C**
- For Ramadan fasting, consider consuming the pre-dawn meal (*Suhor*) as late as possible. **E**
- Carbohydrate counting at the pre-dawn and sunset (*Iftar*) meals enables the rapid-acting insulin dose to be matched to the carbohydrate intake. **C**
- Maintain hydration by drinking water and other non-sweetened drinks at regular intervals during non-fasting hours. **E**

3 | BREAKING THE FAST

- Break the fast immediately, regardless of the timing, if hypoglycemia occurs. This applies to symptomatic and asymptomatic hypoglycemia (blood glucose levels [BGL] <70 mg/dl or 3.9 mmol/L). **E**

3.1 | Principles of care

- It is suggested that care for young people with T1D during fasting be undertaken by experts in the management of diabetes in this age group. **C**
- Regular supervision by health-care professionals during the month of Ramadan and periods of fasting in other religions is necessary to minimize potential risks including hyperglycemia, hypoglycemia, ketoacidosis, and dehydration. **C**

3.2 | Medico-religious recommendation

- We suggest that a consensus on the minimum age of fasting needs to be established by task-force members with knowledge and interest in religious fasting. This should be endorsed by religious scholars to unify rules on fasting and exemption. **E**
- Proper understanding of religions' rules on fasting and sickness, which allows individuals with medical conditions to not fast, is important. Liaison with religious scholars should help to persuade those who do not qualify for fasting and avoid their feelings of guilt. **E**

4 | GENERAL RULES OF OBSERVING FASTING IN DIFFERENT RELIGIONS

Fasting is advised, with variable rules, in healthy adults and adolescents in different religions. A common purpose of fasting in these religions is to gain self-restraint, arouse spiritual consciousness, and better understand the plight of the poor and hungry. In this section, general rules and religious guidance on observing and breaking fasting in different religions are given, with emphasis on potential effects on health and glycemic outcomes in children and adolescents with T1D who choose to fast.

4.1 | General rules of Islam on Ramadan fasting

Ramadan fasting is one of the five pillars of Islam and is obligatory for all healthy adult and adolescent Muslims from the time of completing puberty.[1] As per the Islamic rules and guidance from *Sunnah* (the way of prophet Mohamed), an individual becomes subject to *Shari'a* rulings that apply when specific features of puberty are attained.

Approximately 1.9 billion Muslims celebrate the ninth month of the Hijri (lunar) calendar notable for Ramadan fasting all over the world.[2] The Epidemiology of Diabetes and Ramadan (EPIDIAR), a population-based study conducted in 13 countries and involving almost 13,000 adults with diabetes, showed that 78.7% of individuals with type 2 diabetes (T2D) and 42.8% of those with T1D fast for at least for 15 days during Ramadan. Saudi Arabia had the maximum number of individuals with T1D who chose to fast.[3]

The duration of fasting during Ramadan varies based on geographical location and season but is mandated to be between dawn and dusk. During this period, people who fast abstain from eating, drinking, use of oral medications, and smoking. There are no restrictions on food or fluid intake between dusk and dawn.[1,4] Fasting during Ramadan is not intended to bring excessive difficulty or cause any adverse effect to the individual. Islam has allowed many categories of people to be exempted from fasting; for example, menstruating,

pregnant or breastfeeding women, prepubertal children, the elderly, individuals with any acute or chronic illness in whom fasting would be detrimental to health, individuals with an intellectual disability, or individuals who are traveling.[1] These principles formed the basis of all the consensus statements by several groups.[5–7] The provisions of *al-Fitr* (i.e., *Not to observe the fast*) in Ramadan apply if there is any sickness, according to the Almighty saying: "Whoever of you is sick or on a journey, and some of the other days, and on those who support him, ransom poor food."[1] Therefore, if a person fasts and experiences harm or serious hardship while fasting, he/she may be committing a sin.[4]

Various beliefs exist regarding diabetes management practices during Ramadan. In a study of fasting during Ramadan that included 800 individuals with diabetes, 67% indicated that pricking the skin to measure BGLs breaks the fast.[8] Such a belief might endanger individuals with diabetes and predispose them to acute complications. Medical counseling and liaison with Islamic scholars can help correct wrong interpretation as well as understanding and ensure safer fasting. Although some experts would consider fasting, particularly during Ramadan, a practice at high risk for metabolic deterioration, recent studies have demonstrated that individuals with T1D can fast safely during Ramadan, provided they comply with the fasting-focused management plan and are under close professional supervision.[6,9]

4.2 | Relevant rules of Christian "Orthodox" fasting

The Eastern Christian Orthodox Church is the second-largest Christian church, with ~300 million members.[10] Orthodox Fasting (OF) is a basic and traditional component of the religion, practiced by a large proportion of the Orthodox population.[11] OF includes three main fasting periods: 40 days prior to Christmas, 48 days prior to Easter, 14 days prior to Assumption, along with the fasting period prior to the feast of the Holy Apostles (lasting from 0 to 30 days depending on Easter feast), three other daily feasts (January 5, August 29, September 14), as well as every Wednesday and Friday. Individuals 18–59 years old are expected to fast during these periods.

OF is a kind of periodical diet which recommends abstaining from meat, dairy products and eggs for about 180 days annually, and also abstaining from fish for 155 days. The diet during periods of fasting is characterized by increased consumption of cereals, legumes, fruits, vegetables, nuts and seafood. For this reason, it may be considered as a vegetarian dietary pattern, where fasting and non-fasting periods alternate, sharing common features with the classical Mediterranean Diet.[11,12]

Studies on OF followers conducted in three different countries (Greece, United States, and Egypt), reported low total energy intake, low fat (total, saturated and trans), low animal and high vegetable protein intake, high complex carbohydrate and fiber intake, high vitamin C, folate and magnesium intake, low calcium and vitamin D intake during different fasting periods.[13,14]

The OF meal plan tends to be high in carbohydrate content. Thus, it is advisable for people with T1D to choose carbohydrates with a low glycemic index, and consume them in combination with fiber, proteins (legumes, seafood) or fats (olive oil). Rye, barley, oats, brown rice, quinoa or amaranth are also suitable.[15]

Although data on the effect of OF diet on metabolic health are heterogenous, a potential benefit on lipid profile has been suggested, whereas there are no data on the effects on cardiovascular and musculoskeletal outcomes. Negative aspects of OF, primarily attributed to dietary limitations of specific vitamins (D and B12) and minerals (calcium and iron), should not be ignored, and relevant guidance might be provided to people following OF by health care professionals.[13]

4.3 | Relevant rules of Yom Kippur and other fasts in Jewish law

Yom Kippur fasting is a major fast and the holiest day in the Jewish religion and calendar.[16] It is obligatory for all healthy adult and adolescent Jews from the age of 13 years in males and 12 years in females. All observant and most non-observant Jews practice this 25 h long fasting. It starts at dusk (end of the ninth of Tishrei—first month of the Jewish lunar year) and ends on the following day (10th of Tishrei) at sunset.[16] The activity during this fast involves mostly prayer and soul searching within synagogues. Jewish law includes five other days of fasting between dawn and dusk, and these are mostly practiced only by observant Jews.

During fasting, Jews abstain from eating, drinking, and smoking. Fasting is not intended to cause any adverse effect to the individual.[17] Jewish law allows many categories of people to be exempted from fasting; for example, prepubertal children, women in and around delivery days, individuals with illnesses in whom fasting may be detrimental to health, and individuals with an intellectual disability.[17] Jewish law defines an intermediate state where people who need to break their fast due to health reasons can intermittently eat small portions of 30 g in line with a scheduled time plan.[16]

Various approaches for diabetes management during fasting have been used. Initially, prior to the era of glucometers and CGM, people with diabetes were exempt from fasting. In the last two decades, several studies showed that insulin dose adjustments and close monitoring may enable safe fasting for individuals with T1D.[18–21] Jewish law indicates that specific medical counseling and liaison with Jewish legal scholars should facilitate and help to ensure safer fasting for the individual.[19–21]

4.4 | Fasting in Hinduism, Buddhism, Jainism and other religions

Fasting is also common in other religions in the world. It is well known that followers of Hinduism, Buddhism and Jainism believe that the act of fasting would result in the spiritual transformation of the individual or community.

In Hinduism, different forms of fasting are frequently practised throughout the year. Fasting is not considered an obligation, but a

spiritual and moral act, the aim being to purify the body and mind to acquire self-restraint and divine grace. There are different forms of fasting which vary according to personal, family and community beliefs, which may be strict and difficult to follow, or relatively easy and readily amenable to modifications. The fasting period can be for a single day, weekly (on specific day/s throughout the year), bi-monthly (*Pradosha*—13th day of every fortnight of the Hindu calendar), monthly (*Ekadashi*—11th day of the Hindu lunar month, and *Purnima*—the full moon day). Longer fasting periods may last 9 days and are followed once or twice a year (*Navratras*), or of 1-month duration (*Kartik month*). Variability exists according to timing, duration and type of food intake, including no food and water intake, only water allowed; fruit and milk allowed, and broken rice or millets allowed.[22]

In Buddhism, while fasting is generally practiced by monks, lay people may fast voluntarily as part of a personal spiritual observance. Buddhist Lent is the fast and feast observed for three lunar months every year during the rainy season, when Buddhists fast for a 12-h period, from noon to midnight, followed by feasting for 12 h from midnight to noon.[23] Some devout lay Buddhists also follow the rule during special days of religious observance when one must not eat after the noon meal. The duration of fasting can vary from three (*sanzhai*) to 6 days (*liuzhai*).[24] In the first half of the first, fifth, and ninth months, a continuous long fast (*changzhai*) is also observed.

Fasting is similarly prevalent in Jainism, observed during festivals, holy days, birthdays and anniversaries. There are several types of fasts, varying from 24–36 h to several days and months. *Paryushan* is the main festival during the monsoons, which usually lasts eight or 10 days, respectively, in the Swetambara and Digambara Jain tradition (the two main sects of Jainism).[25] Digambar Jains usually will not consume food and/or water (boiled) more than once in a day; while Shwetambar Jains drink only boiled water during their fast days. Many Jains observe a type of fasting by abstaining from food and water after sunset. *Varshitap* (year-long fast) is a type of fasting in Jainism where devotees fast for 13 months and 13 days, in which they fast completely on alternate days and eat a limited diet between sunrise and sunset on the other days.

The Bahais fast for 19 days in the month of Ala (March), when no food or water is consumed from sunrise to sunset by persons 15–70 years old. In Taoism, fasting is observed in the form of "*Bigu*," where grains are avoided.

5 | WHY GUIDELINES ON FASTING FOR YOUNG PEOPLE WITH DIABETES ARE NEEDED?

Many reviews, consensus statements, and expert opinions detailing the principles of diabetes care during fasting (especially during Ramadan) have been published.[5–7,26–28] A comprehensive guide has been developed by the International Islamic Fiqh Academy, along with the Islamic organization of health sciences, after a thorough literature review of possible risks to people with diabetes associated with Ramadan fasting. Among defined risk stratification groups, T1D is considered to be a very high-risk group.[29,30] However, this document is not specific to young people with diabetes, and overall studies on religious fasting in this population are limited.[31]

A survey by Elbarbary et al. highlighted variations among physicians, from 16 predominantly Muslim countries, in the management of children and adolescents with T1D. There are substantial variations in the perceptions, beliefs, general management, and the practice of insulin therapy in this age group during fasting.[32] The survey also highlighted limitations related to relying on data on the safety and metabolic impact of fasting based on studies conducted in adults with T2D.[32] Furthermore, there is minimal literature on fasting-related issues in religions other than Islam.

6 | SHOULD ADOLESCENTS WITH T1D FAST DURING RELIGIOUS OBSERVANCES?

In many diabetes centers managing Muslim populations, healthcare professionals agree that adolescents can fast if they have reasonable glycemic control, good hypoglycemia awareness, and the willingness to frequently monitor their BGLs during fasting.[33] A recent survey indicated that almost 80% of physicians looking after children and adolescents with diabetes would allow them to fast if they wished.[32]

7 | PRE-FASTING DIABETES EDUCATION

Pre-fasting assessment and education are vital to ensure the suitability and safety of fasting in young people with diabetes. Many diabetes units run special education sessions prior to the month of Ramadan to ensure safe fasting.

Strategies for pre-fasting diabetes education and assessment include the following:

1. Fasting-focused education, including nutrition, physical activity, and insulin dose adjustment, as well as emergency management of hypoglycemia, hyperglycemia, and diabetic ketoacidosis (DKA).
2. Medical assessment including evaluation of hypoglycemia awareness.
3. Optimization of glycemia before fasting to reduce the potential risks associated with fasting and minimize glucose fluctuations.
4. Frequent SMBG, or the use of real-time CGM (CGM)/isCGM, along with training on how to interpret readings and actions to take.
5. The requirement is to immediately breakfasting to treat hypoglycemia or prevent acute complications.

The lack of pre-fasting assessment and proper diabetes education are major obstacles for safe fasting in people with T1D.[32,34] Eid et al. showed that an educational program consisting of weekly sessions before and during Ramadan, enabled people with diabetes to fast safely, with a reduced number of hypoglycemic events per month.[35] A systematic review showed that Ramadan-focused diabetes education in T2D resulted in a substantial reduction of hypoglycemia and

improvement in HbA1c.[36] Structured education has also been associated with a 61% decrease in DKA risk in adults with T1D.[37]

The dose adjustment for normal eating (DAFNE) education program highlights the importance of flexible dosing, carbohydrate counting and matching insulin to carbohydrate intake.[38] This, together with rtCGM or isCGM, can help people with uncomplicated T1D to safely fast during Ramadan.[39,40] In a study from Kuwait, people with T1D using CGM and provided with DAFNE training had a reduced incidence of hypoglycemia during Ramadan compared with the pre-Ramadan period. No episodes of severe hypoglycemia, DKA, acute kidney injury, or hospitalization occurred during Ramadan, including no evidence of increased glucose variability.[39,40] Other studies demonstrated that individuals with T1D who received Ramadan-focused education showed more willingness to fast, since they were more capable of managing their diabetes, and they had better glycemic outcomes and fewer complications.[41,42]

Qualitative studies suggest that structured Ramadan-focused education needs to be developed and implemented in clinic practice.[38,41,43] The DAR practical guidelines 2021 also suggested that individuals with diabetes wishing to fast and receiving pre-Ramadan assessment and education, should fast for a few days during the 2 months preceding Ramadan.[9]

In summary, wider implementation of fasting-focused education for both individuals with T1D and T2D, especially those on insulin therapy, is of paramount importance.

8 | TELEMEDICINE

Based on the growing number of technologies that support diabetes care, telemedicine has been proposed as an important solution to meet the need of expanding care for the benefit of people with diabetes, while improving efficiency and containing costs.[44] During the COVID-19 pandemic, telemedicine and telemonitoring have shifted from an aspirational goal to a de facto standard of care for diabetes management.[45]

Limited studies have investigated the role of telemedicine in the management of diabetes during Ramadan or other religious fasting, especially in adolescents with T1D.

In 2020 and 2021, the Holy Month of Ramadan coincided with the COVID-19 pandemic and lockdown. Limited access to healthcare and the continuous need for diabetes assessment and consultation before and during Ramadan highlighted the urgent need for digital health solutions in diabetes care. The DAR Global Survey on 1483 Muslim participants with T1D showed that 26.8% of those aged <18 years and 73.2% of those aged ≥18 years fasted during Ramadan during the 2020 COVID pandemic.[46]

When comparing the short-term benefits of a telemonitoring-supplemented focused diabetes education with education alone in individuals with T2D who fasted during Ramadan, frequency of hypoglycemia was lower in the telemonitored group.[47] Similarly, the "Making Ramadan Fasting A Safer Experience (MRFAST)" study showed reduced episodes of hypoglycemia and greater reduction in HbA1c in participants with T2D assigned to the telemonitoring group compared to the control group.[48] Participants viewed telemedicine as a more convenient alternative, although technological barriers remain a concern. A prospective study assessed the role of a 24-h Helpline Service for people with diabetes during Ramadan and supported its key role in promoting safe fasting and reducing unnecessary hospital visits and admissions.[49] More than half of the 927 calls were queries related to glucose monitoring data and insulin dose adjustment in T1D.

Overall, telemonitoring offers an attractive option for managing diabetes during Ramadan and other religious fasting, but further data in adolescents with diabetes are needed.[50]

9 | PHYSIOLOGY OF FASTING

In healthy individuals, during fasting circulating BGLs tend to fall leading to decreased insulin secretion. In addition, levels of glucagon and catecholamines rise, stimulating glycogenolysis and gluconeogenesis.[51] In the early hours of fasting, glycogenolysis meets the glucose requirements of the body. This is followed by gluconeogenesis, and later ketogenesis, if the duration of fasting is prolonged. Similar responses, albeit to a lesser extent, occur during the intermittent fasting that occurs during Ramadan.

In people with T1D, hypoglycemia that occurs during fasting may not elicit an adequate glucagon response.[52,53] In addition, individuals with autonomic neuropathy can have defective epinephrine secretion to counteract hypoglycemia.[54] In individuals with T1D fasting during Ramadan or other religious observances, abnormalities in the counter-regulatory hormones (glucagon, cortisol and catecholamines) may also be present due to disruption of the normal circadian rhythms and the sleep-wake cycle. In addition, there is risk of hypoglycemia associated with exogenous insulin treatment during fasting with changes in meal timing.[53]

Several studies have focused on the changes in glucose homeostasis during Ramadan fasting. In a study in young adults without diabetes[55] using CGM 1- to 2 weeks before, in the middle and 4 to 6 weeks after Ramadan, an increase in the hyperglycemic area above 140 mg/dl was noted after Ramadan, compared with both before and during Ramadan, along with increased glucose variability.[55] However, limited data are available on the safety and metabolic effects of fasting in children and adolescents with T1D.[3]

In a study assessing the impact of Ramadan fasting on resting metabolic rate (RMR), activity, and total energy expenditure (TEE), fasting was associated with reduced physical activity and reduced RMR, without an overall reduction in TEE. Ramadan differs from both prolonged and short-term starvation, as the former decreases RMR, whereas short-term starvation may increase RMR, and this has been attributed to a rise in norepinephrine concentrations.[56]

10 | PSYCHOLOGY AND ATTITUDE TOWARD FASTING

Many adolescents with T1D prefer to fast to feel equal to their peers without diabetes.[57] Fasting may boost their self-esteem and make

them happier as they feel "mature and capable" in fulfilling their religious obligations. However, considering the risk of acute metabolic complications in individuals with T1D, they are often advised not to fast.[5–7,26,28,58] Despite the fact that having diabetes grants an exemption from fasting, a large number of youth with diabetes are passionate about Ramadan, and undergo fasting based on social and cultural reasons and a religious sense of fulfillment.[3,57] Young people with diabetes may often fast without the knowledge or approval of their physicians.[59]

Predictably, there is a general fear among persons with T1D and their health-care providers about the use of insulin therapy during the fast, due to the increased risk of hypoglycemia.[60] Hypoglycemia during the daytime is the most disliked complication as its treatment entails the intake of carbohydrate and therefore leads to breaking the fast prematurely. The interruption of fasting may induce a sense of guilt and failure.[61] Data indicate that the majority of Muslim adolescents and older children with T1D are able to fast during Ramadan, with a high proportion of them encouraged by their parents to do so.[61] Their expectations of developing complications are realistic, but they underestimate the deterioration in glycemic control during the month. It is reassuring that the majority agree to break their fast should complications arise, which makes fasting safer for them.

The DEAR program (Diabetes Education and medication Adjustment in Ramadan) aimed to optimize glycemic control prior to Ramadan, and provide risk assessment, preparation, monitoring and intervention pre-, during and post-Ramadan.[62] The program was also initiated to focus on covering the relevant religious and medical aspects through engaging a religious leader and Muslim healthcare professional team. The study highlighted that deficiencies in knowledge among healthcare professionals regarding Ramadan fasting can lead to people with diabetes choosing not to inform their healthcare team that they will fast, particularly in Muslim minority countries.[62]

Depending on where the adolescents live, they often attend school for the whole day, and partake in after-school activities, including sports, during Ramadan, even though they experience sleep disturbances and changes to routines, with late-breaking of the fast and waking early to have the pre-dawn *Suhoor*. For adolescents with T1D, fasting adds more challenges, especially for those living in Muslim minority societies, where there may not be adjustments made to school and sports schedules, particularly when the hours of fasting are longer (summers).

The psychological effects of fasting during Ramadan can vary. Both healthy individuals and people with diabetes can experience opposing psychological outcomes for different reasons, including the changes that accompany the practice of fasting.[63] Further research is needed to assess the psychological effects of fasting during Ramadan in adults as well as adolescents with T1D or T2D.

11 | FASTING: POTENTIAL COMPLICATIONS AND SAFETY

Potential risks associated with fasting are hyperglycemia, hypoglycemia, DKA, thrombotic episodes, and dehydration.[5–7] Although most of the available data are based on adult studies, an individualized approach, close monitoring of BGLs and weekly follow-up with the medical team is the best approach to prevent acute complications in both adults and young people with diabetes.[64]

12 | IMPACT ON GLYCEMIC OUTCOMES

Data on the impact of Ramadan fasting on glycemic outcomes are based on few small studies with inconsistent results. Some studies in children with diabetes demonstrated a significant improvement in fructosamine levels, whereas others showed no changes, or even an increase in HbA1c levels.[57,61,65–68]

Some studies[3,68] have shown that Ramadan fasting in individuals with T1D might predispose to acute complications, although this has not been confirmed by others. Overall, fasting can be considered a safe practice if people with diabetes monitor BGLs frequently and break the fast when hypoglycemia or marked hyperglycemia occur[18,58,64,69,70] Besides, Ramadan fasting has been found safe when pre-fasting medical assessment, focused education, appropriately adjusted insulin regimens, diet control, and management of daily activities have been implemented in individuals with stable diabetes control and no comorbidities[57,68,70] Studies have shown that adolescents are able to fast for several days during the Ramadan month,[71,72] but unplanned fasting may predispose to hypoglycemia and hyperglycemia with or without ketosis.[28,59]

13 | ACUTE COMPLICATIONS

13.1 | Hypoglycemia

Hypoglycemia is a major complication of fasting. The EPIDIAR study of 1070 adults with T1D reported that fasting during Ramadan increased the risk of severe hypoglycemia by 7.5-fold. During Ramadan, 2% of people with diabetes experienced at least one episode of severe hypoglycemia requiring hospitalization.[3] In a pediatric study symptomatic hypoglycemia resulted in breaking the fast on 15% of the days.[72]

In addition, CGM data have shown wide BGL fluctuations during fasting and eating hours and episodes of unreported hypoglycemia.[72] The frequency and duration of hypoglycemia, hyperglycemia, and severe hyperglycemia were significantly higher in adolescents with T1D who had pre-Ramadan suboptimal than those with good glycemic control.[73] In a retrospective study of 50 children and adolescents with T1D (age 12.7 ± 2.1 years), those with HbA1c >8.5% had more frequent episodes of hypoglycemia than those with HbA1c ≤8.5%.[74]

Hypoglycemia has been typically encountered during the hours preceding *Iftar*.[75] Young adults with suboptimal management of T1D experienced wide fluctuations in glucose levels between the fasting and eating hours, with a greater tendency toward hyperglycemia.[76]

13.2 | Breaking the fast due to hypoglycemia

Monitoring BGLs during fasting is essential to predict, prevent, and treat hypoglycemia. It is of paramount importance that BGL is checked if any symptoms suggestive of hypoglycemia are experienced, so that the fast is interrupted promptly. However, some young people may not be willing to break their fast, particularly if hypoglycemia occurs close to sunset (time to end the fast for the day), and this may predispose them to a severe hypoglycemia. A study of 33 children with T1D in Bangladesh showed that only 3 out of 13 children broke their fasting following onset of symptoms of hypoglycemia.[77] However, in another study[61] most children and adolescents were willing to terminate their fasting when hypoglycemia occurred, regardless of the time of the day. Education might persuade young people with diabetes to break the fast when hypoglycemia occurs.

13.3 | Diabetic ketoacidosis

Fasting increases glucagon levels and accelerates lipolysis and ketosis. These pathophysiological changes, in conjunction with fasting itself, may lead to metabolic decompensation in people with diabetes. Episodes of DKA have been reported during Ramadan fasting.[78,79] Detection of euglycemic ketosis during fasting requires evaluation of acid–base state, blood glucose and ketone values (ideally blood ketone measurements, if available) to differentiate DKA from ketosis due to prolonged fasting.[80] See ISPAD 2022 Consensus Guidelines Chapter 12 on Sick Day Management in Diabetes for further details on ketosis monitoring.

14 | INSULIN MANAGEMENT DURING FASTING

Knowledge of insulin action, interpreting glucose values and adjusting insulin doses for *Iftar* and *Suhoor* meals, is a prerequisite for safe Ramadan fasting. Based on clinical experience, different recommendations on how to adjust the type, dose, and timing of insulin in adults have been suggested.[69,81,82] However, clear evidence-based guidelines on insulin adjustment for adolescents with T1D are lacking.

Current recommendations for people on multiple daily injections (MDI) include a reduction of the total daily dose (TDD) of insulin to 70%–85% of the pre-fasting TDD[27,82] or 60%–70% of the pre-fasting dose of basal insulin.[7] For people on continuous subcutaneous insulin (CSII), a reduction of the basal rate of insulin infusion by 20%–40% in the last 3–4 h of fasting is recommended.[7] The South Asian Guidelines for Management of Endocrine Disorders in Ramadan recommend reducing basal insulin by 10%–20% during the fast days.[79,80] However, these recommendations are not based on data from large cohort studies or randomized controlled studies. Some studies have not shown a reduction in frequency of hypoglycemia with reduction of basal insulin in MDI and CSII regimens, although this has not been confirmed by all studies.[83,84] A suggested guide for adjustment of insulin dosages is given in Figure 1.

15 | INSULIN REGIMENS FOR ADOLESCENTS WITH T1D

Management of diabetes during fasting should be discussed on an individual basis, depending on access to different insulins and technology. Once fasting has started, insulin dosing should be regularly adjusted based on the results of glucose monitoring. Frequent BGL measurement is essential. MDI and CSII are the preferred regimens in young people with T1D during Ramadan.[85] In some regions, treatment with two or three daily injections with NPH and short-acting insulin may be used. Use of premixed insulin regimens require fixed intake of carbohydrates at set times and is not advised.

16 | BASAL-BOLUS INSULIN TREATMENT

16.1 | Basal insulin

16.1.1 | Long-acting insulin analogs

Insulin analogs have been safe for the management of well-controlled young people with diabetes during a fasting period of 17–19 h. A significant decline in glucose levels, with periods of hypoglycemia, is seen mostly near the end of the fasting period, although no episodes of severe hypoglycemia have been reported.[7,57,65,69,72,86,87] It is recommended that during Ramadan, the pre-Ramadan basal insulin dose should be reduced by 20%, when given in the evening.[5,27,57,68–71,87] When taken at *Iftar*, a further reduction may be needed—up to 40% of the pre-Ramadan basal dose.[7,88] Further individualized adjustment of the dose needs to be considered.

16.1.2 | NPH insulin

Based on the pharmacodynamic profile of NPH, there is a considerable risk of mid-day hypoglycemia and end-of-the-day hyperglycemia. Reduction of the dose is needed to prevent hypoglycemia, at the possible expense of higher BGLs at the end of the day.

16.2 | Bolus insulin

In most studies, the pre-*Iftar* and pre-*Suhoor* rapid-acting insulin doses are equal to the pre-Ramadan lunch and dinner doses, respectively. In some reports, the pre-dawn dose is reduced by 25%–50%,[7] depending on the carbohydrate content of the meal and the pre-meal BGL. In an adult study, the use of rapid-acting insulin analogs was associated with fewer hypoglycemic events and an improvement in postprandial glycemia compared with regular insulin.[89] Higher BGLs may require

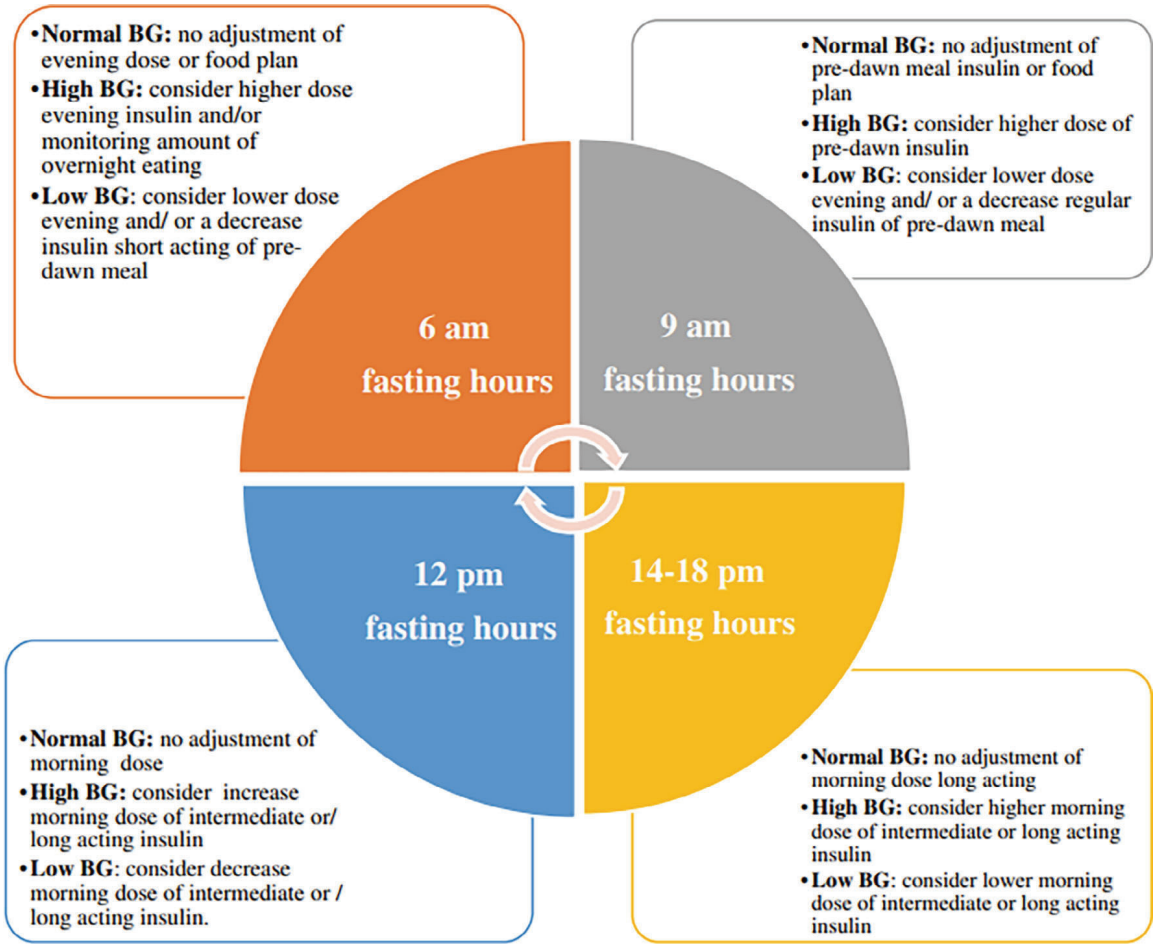

FIGURE 1 Schematic adjustments of insulin dose and/or food considerations during fasting hours

an additional dose of insulin administered as a correction dose, which is usually based on the pre-Ramadan correction factor.

16.3 | Twice daily insulin treatment

Two daily injections of NPH and regular insulin allow less flexibility in lifestyle and nutrition with more risk of hyperglycemia and hypoglycemia; therefore, their use is strongly discouraged. Owing to the NPH peak effect, dose adjustment for a 12–16 h period of fasting is more challenging.[84] Children on a twice-daily insulin regimen are much more prone to experience hyperglycemia with/without ketones than those on a basal-bolus regimen.[84] Using twice-daily insulin regimens during Ramadan requires more dose adjustments, taking the usual morning dose before the sunset meal and only short-acting insulin at the time of their dawn meal.

16.4 | Premixed insulin

Premixed insulin is not recommended in people with T1D. Premixed insulin given twice daily requires fixed intake of carbohydrates to coincide with the peaks of insulin activity. During fasting, it is difficult to properly adjust carbohydrate intake in *Suhoor* and *Iftar*; therefore the use of premixed insulin is not advised.[9] However, many individuals with T1D, especially in regions where basal-bolus insulin is not prescribed or available, use premixed insulin. These individuals can either refrain from fasting, but those who still want to participate in Ramadan fasting, should discuss with their physicians before Ramadan starts, regarding the safety of using premixed insulin while fasting and the importance of blood glucose monitoring to detect hypoglycemia.

17 | INSULIN PUMP THERAPY

The use of insulin pumps can facilitate insulin adjustment and decrease the risk of hypoglycemia and hyperglycemia during fasting.

17.1 | Basal rate

Lowering the basal insulin infusion rate temporarily or suspending it, can help people with T1D to avoid major hypoglycemic events and

TABLE 1 List of commonly eaten food during the month of Ramadan

Food	Serving size	Carbohydrate (g)
Fruits and vegetables		
Dried figs	2 figures (28 g)	16
Fresh dates	1 date (19 g)	6
	3 dates (57 g)	18
Dried dates	1 date (6 g)	4
	3 dates (18 g)	12
Dried apricot	1 half (6 g)	2
	8 halves (48 g)	17
Sultanas	Snack pack (40 g)	30
Dried barberries	1/4 cup (37 g)	20
Cakes, pastries, and sweets		
Chocodate Arabian delights (chocolate-coated dates with nut inside)	1 piece (11 g)	7
Mouhalabieh (milk flans)	1 cup (200 g)	30
Galactobureko (filo custard pastry, syrup soaked)	1 piece	28
Baklava	1 piece (50 g)	26
Turkish delight	1 piece (18 g)	15
Kanafeh	1 square, 6 tablespoons (120 g)	40
Halva (nut butter-based, e.g., tahini)	2 tablespoons, (50 g)	22
Ghraybeh (butter cookies)	1 cookie (15 g)	7
Ma'mool/maamoul/ma'moul (cookies stuffed with walnuts/dates)	1 cookie (35 g)	23
Basbousa (sweet semolina cake soaked in syrup)	1 slice (30 g, 3 cm × 3 cm)	14
Sekerpare (butter cookie soaked in syrup)	1 piece (18 g)	16
Tulumba (fried dough soaked in syrup)	1 piece (35 g)	37
Lokma (sweet fried dough)	1 ball (13 g, 2 cm diameter)	10

improve glycemic control during fasting.[64,68,70] In most studies, the basal insulin rate is reduced by 10%–15% during the hours of fasting; with some suggesting a reduction up to 40% toward the end of the day.[70,72,73,90] However, one study did not show any difference in hypoglycemia frequency if the basal rate is reduced.[83]

17.2 | Bolus

Insulin boluses covering the predawn and sunset meals have been either increased[70] or unchanged as per the pre-Ramadan insulin-to-carbohydrate ratio and insulin sensitivity factor.[72,75,90] In studies in young people on CSII, none developed severe hypoglycemia or DKA during Ramadan fasting.[64,70,72,75,83,90]

The benefits and risks of CSII or MDI during Ramadan were recently assessed by two systematic reviews and meta-analyses.[53,91] Loh et al.[53] pooled data from 17 observational studies involving 1699 persons treated with either CSII or non-CSII regimens and concluded that the CSII regimen was associated with lower rates of severe hypoglycemia and hyperglycemia, but higher rates of non-severe hyperglycemia than MDI regimens. These findings suggest that appropriate selection of individuals, with regular adjustments of the basal insulin rate and intensive glucose monitoring, might mitigate the hypoglycemia risk during Ramadan. However, analysis of observational studies[91] using CSII versus MDI during Ramadan did not show any differences in weight, HbA1c or lipid levels.

17.3 | Sensor-augmented pumps

Fasting during Ramadan is feasible with sensor-augmented pumps (SAP), with adequate counseling and support.[65,84] Significantly, fewer episodes of hypoglycemia have been observed with use of the predictive low-glucose insulin suspend algorithm in 60 adolescents with T1D.[90]

18 | THE ROLE OF NEWER INSULINS

Although some experience with newer insulins in adults with diabetes has been reported, further data are needed in the pediatric population to establish clear guidance around their use. These include more concentrated insulin formulations (insulin glargine U300) and the newer basal insulin degludec, with flatter pharmacodynamic profiles.[92]

Insulin degludec is approved for clinical use from the first year of age and is associated with lower rates of nocturnal hypoglycemia,

more flexibility in timing of insulin administration and better quality of life compared to other basal insulins.[93–95] These advantages might be of utmost importance especially during fasting.

The ORION study,[96] a prospective, observational, international multicenter study, evaluated the safety and effectiveness of Glargine 300 units/ml in insulin-treated adults with T2D before, during and after Ramadan in a real-world setting, found a low risk of severe/symptomatic hypoglycemia and improved glycemic control.

Hassanein et al.[97] showed that in adults with T2D during fasting, insulin degludec/insulin aspart (IDegAsp) is effective, safe and well tolerated.

19 | NUTRITION MANAGEMENT DURING RELIGIOUS FASTING

19.1 | Pre-fasting nutrition education

Pre-fasting nutrition assessment and education is essential to ensure the safety of young people planning for Ramadan or other fasting. An individualized meal plan is required, based on energy requirements, commonly eaten/permitted foods during the fast, timing of *Suhoor* and *Iftar* meals, insulin regimen, and exercise pattern. Ongoing monitoring of BGLs with appropriate insulin adjustment is necessary to prevent hypo- and hyperglycemia. It is recommended that fluids, such as water or non-sweetened fluids, be consumed at regular intervals in the non-fasting hours to prevent dehydration.

19.2 | Meal-time routines during Ramadan

Ramadan fasting represents a major shift in meal timing and content and daily lifestyle and exercise patterns. The two main meals are *Iftar* (usually eaten 6–7:30 p.m.), and *Suhoor* (usually consumed between 3 and 5.30 a.m.). Mealtimes depend on the time of sunrise and sunset. The predawn meal should be eaten as close to dawn as possible, to minimize the fasting period. In addition, a late evening meal or supper is commonly eaten before bed (about 10 p.m.). This usually contains traditional sweets. A snack such as milk and dates or juice may initially be taken before *Iftar* to break the fast.

19.3 | Guidelines for nutritional care and meal planning

The nutritional composition of food eaten during Ramadan is different from the rest of the year. Commonly eaten foods are shown in Table 1.

Significant changes in nutrient intake, with higher fat and sugar intake, during Ramadan is reported in adolescents with T1D.[98] It is recommended that adolescents with T1D should lower saturated fat and sugar. Low glycemic index (GI) carbohydrates should be the basis of foods consumed at *Iftar* and *Suhoor*. Lean protein and low GI carbohydrates are particularly important at *Suhoor* to enhance satiety during the day. Moderation in traditional sweet intake and fried foods is strongly recommended, particularly at *Iftar*. The *Iftar*, *Suhoor* and other nighttime snacks and meals should be covered by prandial rapid-acting insulin to prevent postprandial glycemic excursions, with education on carbohydrate counting to allow adjustment of the insulin dose to match carbohydrate intake. Daily consistency in carbohydrate intake is necessary for those not familiar with carbohydrate counting. Continuous snacking after *Iftar* should be discouraged. The insulin bolus should be given before the meal; administration during or after the meal is not advisable.[99]

The use of an extended bolus delivered by an insulin pump, where some of the insulin is delivered promptly and the remainder over 2–6 h, enables the insulin bolus to match the glycemic effect of the meal. This is particularly useful for the high-fat meals consumed at *Iftar*.

19.4 | Maintaining healthy weight and lowering of cardiovascular risk factors during Ramadan

It is important to prevent dyslipidemia and excessive weight gain during Ramadan.[66] A diet rich in fruit, vegetables, low-fat dairy products, legumes, and whole grains should be encouraged to reduce adverse changes in lipid profiles and to prevent excessive weight gain.

In children and adolescents with T1D, both weight gain and weight loss have been reported during Ramadan.[69,77] Therefore, an individualized plan with appropriate energy intake to maintain growth and development is required, as well as regular follow-up to monitor and prevent rapid weight changes.

20 | FASTING AND PHYSICAL ACTIVITY

Exercise patterns in adolescents are different from adults, varying from unpredictable play to planned sports. It is recommended that a reasonable level of activity should be maintained during Ramadan fasting, with avoidance of strenuous activities in the hours before sunset, when hypoglycemia is most likely. Exercise patterns vary depending on the geographic region and the need for school attendance. Differences in sleep patterns coupled with fasting in the daylight hours impact the amount and type of physical activity youth participate in. Adolescents without diabetes have been reported to reduce physical activity during Ramadan fasting.[100]

Studies on nutrition and sports management during Ramadan focusing on adolescents are limited. Typically, outside of fasting periods, additional carbohydrate is advised for spontaneous activities to avoid hypoglycemia.[100] During fasting, careful attention to insulin adjustment is required to enable normal levels of physical activity without hypo- or hyperglycemia. Pre-fasting diabetes education should discuss physical activity with a plan for appropriate insulin adjustment, hydration and hypoglycemia treatment as part of individualized care.

A review of studies in healthy adult athletes who participated in Ramadan fasting concluded that changes in training, fluid intake, diet, and sleep patterns can be managed to minimize, but not fully mitigate, the impact on athletic performance.[101] The review concluded that athletes with T1D should consider medical exemption from fasting; however, if an athlete with T1D chooses to fast, an individual plan to optimize performance and ensure safety is needed. Principles of nutritional management for athletic performance in T1D during fasting have been proposed,[102] however, they require adaptation in meal timing for fuel and recovery.

21 | MONITORING OF BLOOD GLUCOSE DURING FASTING

Optimizing glycemic control pre-Ramadan or other religious fasting is an essential measure to ensure safe fasting. Frequent BGL measurements are needed for safe fasting, and this does not violate the observance of Ramadan. The concept among Muslim communities that pricking the skin for BGLs invalidates Ramadan fasting is an incorrect interpretation.[8] This should be strongly emphasized in educational programs. SMBG remains the most widely used method of monitoring, but the use of CGM can greatly facilitate insulin adjustments.

BGL monitoring during fasting is based on the same principles of monitoring outside of fasting, with the times being related to meals, medications and symptoms. To assess adequacy of postprandial BGLs, readings are recommended 2 h after the main evening meal (*Iftar*) and before the predawn meal. A measurement on waking up is essential to enable individuals to judge their basal dose as well as the *Suhoor* meal insulin dose. Testing in the last 2 h of the fasting period is recommended, as there is an increased likelihood of hypoglycemia at this time.[73,75] Additional midday BG monitoring is useful if morning readings are in the low-normal range. Testing is essential when symptoms of hypoglycemia are experienced or suspected.

22 | CONTINUOUS GLUCOSE MONITORING

The use of CGM is becoming the standard of care for people with T1D, but unfortunately these devices are still inaccessible in many parts of the world due to their high cost and lack of national insurance coverage. In a study of 14 adolescents with T1D using CGM, no difference in mean BGLs or duration of hypoglycemia, hyperglycemia, and severe hyperglycemia were found between the Ramadan and non-Ramadan period.[103] Adults and adolescents with T1D show wide glucose fluctuations during Ramadan, with a slow fall during fasting hours followed by a rapid rise in glucose levels after the sunset meal (*Iftar*)[104] These data suggest that efforts should be made to decrease glycemic excursions following *Iftar*, including administering insulin 15 to 20 min before the meal and replacing high GI for healthier, low GI foods.[105]

Beshyah et al.[106] provided a comprehensive demonstration of glucose changes during Ramadan fasting using isCGM in eight individuals with different glucose tolerance status, showing high glucose exposure, wide variation and marked glucose instability after both *Suhoor* and *Iftar*. In a prospective pilot study on 51 children with diabetes, isCGM revealed hypoglycemia in 33% of the days, without episodes of severe hypoglycemia or DKA.[67] In another study in adolescents with diabetes, the use of isCGM showed the daily pattern of hypoglycemia with an incidence of episodes of 0% between 7 and 11 p.m., which increased to 69% from 11 a.m. to 7 p.m.; 65% of these episodes were mild (between 61 and 70 mg/dl), and 8% were lower than 50 mg/dl.[75] These studies suggest that adolescents with T1D could use CGM to fast without any risk of life-threatening severe hypoglycemia or DKA. Multiple devices linked with remote connections are now available, and have a role in remote monitoring, detecting and reducing potential complications during fasting.

23 | FASTING IN YOUNG PEOPLE WITH T2D

There is a global rise in the prevalence of T2D in young people that is associated with the increased incidence of obesity and sedentary lifestyle.[107,108] In 2018 a dramatic rise in the prevalence of T2D was reported in Indonesia, the largest Muslim population in the world.[109] In parallel to this, interest has grown on the impact of Ramadan fasting on the prevention and/or improvement of T2D.

Intermittent fasting is a form of fasting where a person cycles between periods of eating and fasting for religious or non-religious reasons. It has become a popular pattern of eating for weight loss and control of T2D in adults.[110]

Individuals with medical conditions such as T2D are exempted from Ramadan and other fasting in different religions. However, as discussed earlier, the EPIDIAR survey showed that 79% of Muslim people with T2D fast regardless of the possible risk of complications such as hypoglycemia, hyperglycemia, dehydration and thrombosis.[3]

Overall, current evidence suggests safety and a positive impact of intermittent fasting on glycemic and metabolic control of people with T2D, supporting this practice, especially in the low and medium risk groups.[111] When followed under medical supervision, intermittent fasting may reduce body weight, central adiposity and HbA1c.[112] It can also improve insulin sensitivity and markers of cardiovascular disease. However, intermittent fasting can be associated with hypoglycemia in people with diabetes treated with sulfonylureas and insulin.[113] Different conditions in different regions such as weather, duration of fasting and cultural eating habits may contribute to different effects on the metabolic profile of people with T2D who adopt intermittent fasting.[112]

It should be noted that unlike most forms of intermittent fasting, Ramadan fasting involves no intake of water or other fluids during the fasting period. Previous studies suggested that Ramadan fasting may affect metabolic profile by decreasing the frequency and amount of calorie intake, decreased physical activity, fluid restriction and

TABLE 2 Risk groups of people with T2D plan to observe fasting

Very high risk: fasting not recommended • Severe hypoglycemia within the 3 months prior to Ramadan. • Severe hyperglycemia with average fasting or premeal plasma glucose >16.7 mmol/L (300 mg/dl) or glycated hemoglobin (HbA1c) >86 mmol/mol (10%). • A history of recurrent hypoglycemia or hypoglycemia unawareness. • DKA/hyperosmolar hyperglycemic state within the 3 months prior to Ramadan. • Acute illness. • Performing intense physical labor. • Chronic dialysis.
High risk: may choose not to fast • Moderate hyperglycemia (average BGL 8.3–16.7 mmol/L [150–300 mg/dl] or HbA1c 64–86 mmol/mol [8%–10%]). • Significant microvascular or macrovascular complications. • Living alone and treated with insulin or sulfonylureas. • Individuals with comorbid conditions that present additional risk factors such as heart failure, malignancy, renal impairment.
Moderate risk: may choose to fast with caution People with T2D with no complications and HbA1c <64 mmol/mol (8%) treated with lifestyle intervention, metformin, thiazolidinedione (TZD), incretin-based therapies, sodium-glucose cotransporter-2 inhibitors and/or short-acting insulin secretagogues.
Low risk: may choose to fast People with T2D with no complications and HbA1c < 53 mmol/mol (7%) treated with lifestyle intervention, metformin, TZD and/or incretin-based therapies. With encouragement on adequate hydration during non-fasting hours, especially in hot humid environments, to reduce the risk of dehydration and postural hypotension

Source: Adapted from Ibrahim et al 2020.[111]

changes in sleep pattern.[111,112,114–116] Ramadan fasting was found to reduce Fetuin-A levels, a glycoprotein associated with insulin resistance.[117] A recent meta-analysis reported a general reduction in body weight and waist circumference and an overall improvement of metabolic profile markers such as BGLs, HbA1c and lipid levels after Ramadan fasting.[112] In a study in the United Arab Emirates in individuals with T2D not treated with insulin, fasting was not associated with any significant short-term changes in metabolic control, glucose fluctuation or time in hypoglycemia, apart from an initial increase in glucose variability, compared with the non-fasting pre-Ramadan period.[118]

Although adolescents practice Ramadan fasting and other forms of intermittent fasting, the impact of such fasting on glucose biomarkers in this age group has not been adequately studied.[108] However, it has been hypothesized that adolescents with T2D will probably benefit from intermittent fasting similar to adults, given a similar pathogenesis of the disease.[108] Several studies reported that intensive education programs before and during Ramadan could significantly improve and prevent the complications of diabetes such as hypoglycemia.[36,119] However, this kind of support may not always be feasible for Muslim adolescents in Western countries.[120]

23.1 | Recommendations on management of fasting in people with T2D

Successful management of adolescents with T2D during intermittent fasting should aim at achieving the general goals of control of symptoms, reasonable glycemic targets and prevention of acute complications such as hypoglycemia, which is the most common concern for people with T2D.[112] Structured diabetes education can improve glycemic and metabolic outcomes.[36,121] Health care providers should screen individuals with T2D before Ramadan, to assess risks and educate them to improve safe fasting practices.[121]

The American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) consensus recommendations provide comprehensive guidance for person-centred glycemic management in individuals with T2D who observe Ramadan fasting.[111] Pre-Ramadan counseling and clinical assessment should include review of areas such as key characteristics such as age, lifestyle, cultural and socioeconomic factors and presence of comorbidities, with risk stratification.[111] The categories of risk for individuals with T2D who fast during Ramadan range from very high to low-risk individuals, as reported in Table 1.[111]

Management plan during Ramadan can be summarized as follows:

- Identification of the individual's risk category and other risk factors, such a sub-optimal adherence to medications, fear of hypoglycemia, medication side effects and lack of access to medications.
- Regular and more frequent monitoring of BGLs during fasting (especially for those on insulin, insulin secretagogues and high-risk groups), although CGM is *currently not routinely* recommended for individuals with T2D.[111]

The therapeutic options for fasting for people with T2D include: lifestyle management, weight management and adjustment of medications.[111] Guidance on the first two options can be referred to in other parts of this document, in relation to dietary changes and different intensity of exercise, including Taraweeh prayer, where they are encouraged to increase physical activity that improves insulin resistance. However, the recommendations on non-insulin lowering medications can be referred to in the most recent ADA/EASD consensus updated 2019 guidance.[122] The most common non-insulin lowering medication approved for adolescents with T2D is metformin. No dose change for metformin is advised during Ramadan and this drug is generally not associated with risk of hypoglycemia.[111]

23.2 | Future perspectives for management of T2D during fasting

Technology can be used where available to aid in adjusting therapy and improve care and support for adolescents with T2D who intend to fast during Ramadan. Nowadays, food intake, BGL monitoring, medication dosages and exercise time can all be digitalized and accessed remotely.[111] Based on the currently available literature

among young adults, it might be safer to implement fasting programs among well controlled young people with T2D under close observation and medical supervision.[108] Intermittent fasting non-religious programs might be cost-effective, with the potential to minimize the incidence of T2D, preventing young people from developing T2D and protecting them from complications linked to disease and infection.[108] However, there is need for further research to assess how intermittent fasting might impact the health of children and adolescents with T2D (Table 2).

24 | LIMITATIONS OF STUDIES ON RELIGIOUS IN YOUNG PEOPLE WITH DIABETES

Studies on fasting during Ramadan in children and adolescents have several limitations, such as small sample size and retrospective designs, which influence the interpretation of the results. Country-specific differences in physical exercise and schooling demands may also impact study outcomes. As the season when Ramadan occurs changes, conclusions are not universally applicable. The impact of physicians' and diabetes educators' knowledge, attitudes, beliefs, and practices in relation to Ramadan fasting highly influence the education and management of young people with diabetes. In addition, there are limited data on other religious fasting practices in young people with diabetes. Further multicenter studies are needed to increase the understanding of the safe management of Ramadan and other religious fasting in young people with diabetes. However, obtaining the approval of ethics committees to undertake such studies in adolescents and young adults can be difficult. This is particularly challenging because cultural and religion-sensitive issues might arise from such research.

25 | CONCLUSIONS

The management of young people with diabetes during Ramadan and other religious fasting is challenging, due to limited high-quality data in this specific population. Well-designed, randomized controlled trials are needed to determine optimal insulin regimens to minimize glucose fluctuations throughout the fasting and eating hours. Recent developments, such as the use of new insulin analogues, insulin pumps, advanced glucose monitoring devices and telemonitoring might enhance safe fasting in the future. However, these innovations are not universally accessible. At the present time, careful individual assessment and structured diabetes education remain the mainstay of ensuring safe fasting.

AUTHOR CONTRIBUTIONS

AB, DZ, MK and KG contributed to the section of the 'General rules of fasting in different religions'. SS and SA put a draft on the section of 'pre-Ramadan education'. Telemedicine and digital health section were written by SS and AEA. UIU wrote the 'physiology of fasting' section. ABP and SA put a draft for 'psychology offasting section'. UIU and MK drafted the 'impact on metabolic control' section. SS and KG worked on the 'complications of diabetes'. AP and DZ wrote the 'insulin regimens' section while AEA wrote the section of 'insulin pumps'. SA and MK put a draft on the 'nutrition management in Ramadan'. Physical activity in fasting was written by SK and ZK. AEA wrote the section of 'Blood glucose monitoring' and AB wrote the type 2 diabetes section. MLM guided authors on the proper writing of the chapter and revised the final version. AD liaised between authors, divided the tasks, arranged and chaired chapter meetings, put the drafts together and edited each part. All co-authors revised and approved the final version.

ACKNOWLEDGMENTS

Authors acknowledge endorsement of the guidelines by the following societies: the Arab Society of Paediatric Endocrinology and Diabetes (ASPED), the African Society of Pediatric and Adolescent Endocrinology (ASPAE), the Asia Pacific Pediatric Endocrine Society (APPES), the European Society of Paediatric Endocrinology (ESPE), and the Global Pediatric Endocrinology and Diabetes (GPED).

CONFLICT OF INTEREST

None of the authors declared any conflicts of interest that may jeopardize the impartiality of these guidelines.

DATA AVAILABILITY STATEMENT

Data used for chapter writing is available on request.

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How to cite this article: Deeb A, Babiker A, Sedaghat S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Ramadan and other religious fasting by young people with diabetes. *Pediatr Diabetes*. 2022;23(8):1512-1528. doi:10.1111/pedi.13447

Accepted: 24 November 2022
DOI: 10.1111/pedi.13456

ISPAD GUIDELINES

ISPAD International Society for Pediatric and Adolescent Diabetes WILEY

ISPAD Clinical Practice Consensus Guidelines 2022: Management of the child, adolescent, and young adult with diabetes in limited resource settings

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KEYWORDS: adolescents and young adults, children, limited resource countries, limited resource settings, low-income countries, persons with diabetes, resource limited, type 1 diabetes, type 2 diabetes

1 | WHAT IS NEW OR DIFFERENT

This guideline provides updated and consolidated guidance on best-possible care to children, adolescents, and young adults with type 1 diabetes (T1D) and type 2 diabetes (T2D) in widely varying situations when human and medical resources are acutely or chronically limited for any reason.

The management of T1D should be as physiological as possible even in limited resource settings (LRS), to improve care and decrease morbidity and mortality. These recommendations are not aimed at endorsing suboptimal care, but at improving care by making the best possible use of available resources, while constantly endeavoring to reach the next level.

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

The child, adolescent and young adult with diabetes should receive optimal care according to the principles and recommendations described in the respective chapters of the ISPAD 2022 Clinical Practice Consensus Guidelines (ISPAD 2022 CPG) as far as possible. (See Appendix A for the list of chapters).

The following recommendations and suggestions give various options and guidance to provide best possible care when resources are limited, with the acknowledgement that conditions may vary between centers, within the same center depending on finances and facilities, and even from time to time. The recommendations use the American Diabetes Association Evidence Grades, and rely heavily on expert opinion.

2.1 | Introduction

- Suboptimal care of the young person with diabetes (PwD) remains common, even though outcomes improve significantly with awareness and diabetes education. **E**
- Diabetes management in LRS should be as physiological as possible, maximizing quality of life (QoL), preventing acute and chronic complications, and allowing adequate growth and development. **A**
- All PwD should have access to basic diabetes care supplies, including insulin and blood glucose level (BGL) monitoring devices, and diabetes education. The increasing availability and decreasing costs of various insulins and glucometers, as well as increasing communication due to improving technology, have lowered the cost of basic diabetes care and made it more accessible. **E**
- In LRS, co-existing poverty, low rates of literacy, family or community conflict, uncertain safety, discrimination and stigma make families with PwD more vulnerable. The T1D Index attempts to quantify the impact in different regions. **E**
- It is desirable that health care professionals (HCP) provide the level of care according to available resources, while aiming to attain more comprehensive care when local circumstances and facilities improve (Tables 1 & 2). **E**
- All members of the diabetes care team (DCT) should share the same goals and approaches. **A**
- It is desirable that HCP are aware of support available locally, nationally, and internationally; from Governments and non-governmental organizations (NGOs). **E**
- It is suggested that HCP be aware of the latest low-cost diabetes technology and therapy available. **E**

2.2 | Diagnosis, epidemiology, classification, and stages of type 1 diabetes

- The diagnostic criteria for all types of diabetes are based on symptoms and laboratory measurement of BGL. If BGL testing is unavailable, diabetes can be provisionally diagnosed if classical symptoms are present and urine glucose is elevated (and urine ketones are present, if testing is available). **E**
- Registries and data in LRS are scarce, hindering adequate policy decisions and action. It is suggested that steps be taken for improving availability of data. **B**
- Measurement of islet autoantibodies, C-peptide or genetic tests is not routinely recommended for the diagnosis of T1D. They may be selectively done if diabetes type is unclear. **E**
- The diagnosis of monogenic diabetes by genetic testing is becoming more available and affordable. **A**
- Individuals with a first degree relative with T1D have ~15-fold increased relative risk of developing T1D. **A** BGL testing in symptomatic relatives may be helpful for early diagnosis. **B**
- Screening and diagnosing pre-symptomatic diabetes (stages 1 and 2) may not be feasible in LRS, but early diagnosis of symptomatic diabetes (stage 3) is strongly recommended for prevention of DKA and reducing morbidity and mortality. **A**

2.3 | Diabetes education

- Diabetes self-management education (DSME), initial and ongoing, is important for PwD and caregivers, wherever they live in the world. **E**
- Appropriate DSME improves glycemic, psychosocial, acute and chronic medical outcomes. **E**
- It is suggested that education resources be translated into local languages, be visual and tailored to literacy and age. **C**
- Training older role models (experienced PwD and parents of PwD) is helpful in remote areas, as is group teaching at clinics. **E** A separate pediatric diabetes clinic is advisable. **E**
- Organized diabetes meetings and camps during weekends or vacations are helpful for education, reinforcement, reminders, and emotional support for PwD and family members. **E**

2.4 | Insulin therapy

- Physiological insulin replacement using multiple daily injections (MDI) is desirable, in addition to the greatest frequency of self-monitoring of blood glucose (SMBG) available. **E**
- Optimal glycemic targets and QoL can be achieved using low-cost conventional insulins (Regular and NPH) and SMBG, though analog insulins offer some advantages. **B**
- Pre-mixed insulins and two dose regimens are not physiological. They are associated with increased acute and chronic complications, offsetting financial benefits, if any. Hence, these are not desirable for management of T1D and should only be used until other alternatives can be obtained. **E**

TABLE 1 Possible solutions to T1D care in LRS

Constraint	Insulin affordability	Insulin access	Glucometer strip cost	Scarcity of strips	No fridge for insulin	Illiteracy	Lack of educators
Possible solution	Use regular as bolus and NPH as basal	Connect to nearby NGO/ Support group	Connect with company/ Govt/ NGO for low-cost options	Devise effective monitoring patterns and interpretation using available strips	Use options like earthen clay pot in scientific way	Use videos and other visual modes of teaching	Train adults with T1D or caregivers to become coaches

2.5 | Glucose monitoring

- Though glucose monitoring is expensive, achievement of glycemic targets is not possible without regular SMBG. **A**
- If the ideal of 6–10 SMBG tests per day is not possible, at least pre-meals and bedtime BGL testing is suggested for determining appropriate insulin dosing and reducing nocturnal hypoglycemia. Testing 3–4 times on the same day, several days a week, may provide more information than a single daily measurement at different times. **E**
- BGL targets should be individualized: an increased lower BGL limit of 80 or 90 mg/dl (4.4 or 5 mmol/L) may be more practical in LRS to reduce the risk of hypoglycemia. **E**
- Target HbA1c for young PwD should be <7.0% (<53 mmol/mol) without frequent hypoglycemia and/or severe hypoglycemia (SH), although targets may need to be individualized based on circumstances. **A**
- HbA1c should be measured every 3 months, if available and affordable. **E**
- Although infrequently available in LRS, continuous glucose monitoring (CGM) should be used whenever possible, especially in preschool children. **A**
- If constant use of CGM is not feasible, intermittent use of CGM (i.e., once every few weeks), may provide better understanding of glycemic patterns. **E**

2.6 | Nutrition

- Nutritional advice needs to be adapted to cultural, ethnic, and family traditions. **E**
- Visual teaching of portion sizes and carbohydrate counting of local foods, available on several websites, is helpful. **E**
- Food insecurity may worsen glycemia, increase acute and chronic complications, and cause nutritional deficiencies. **C**
- PwD with celiac disease (CD), obesity, dyslipidemia, and hypertension need special attention. **C**

2.7 | Exercise

- Exercise is a key aspect of diabetes management and must be encouraged in every PwD. **A**
- Insulin dosing and/or food intake should be adjusted to safely exercise without hypoglycemia. **A**
- Food should be available during and after physical activities, as needed. **A**
- Exercise should be avoided or minimized, if food is not available. **E**
- Where manual labor or sports are part of the daily routine, it is desirable that the importance of SMBG and food availability are emphasized. **E**
- Predictability and routine are of great value in avoiding exercise-related complications when SMBG is irregular. **E**

2.8 | Hypoglycemia

- Hypoglycemia is common in LRS and is a major impediment to achieving optimal glycemia. **A**
- Education about hypoglycemia for family, friends, school staff, and colleagues is as important as for the PwD, for timely prevention, recognition, and management. **E**
- Reinforcing hypoglycemia education at regular intervals and during sports is suggested. **E**
- MDI insulin regimens are more likely than premixed or fixed dose insulin regimens to prevent hypoglycemia, especially if food insecurity is present. **E**
- Glucagon can be lifesaving and is listed in the WHO's Essential Medicines List (EML). Local advocacy is advised to increase availability of this medication. **E**
- Newer injectable glucagon and nasal spray glucagon are now available – they are easier to use, and may become more widely available with time. **E** They can be suggested, if available and affordable. **E**
- Glucose paste or gel, honey, or other such sugar source applied sublingually or on the buccal mucosa could be lifesaving. **E**
- Availability of health care centers and emergency responders where intravenous (IV) glucose can be given for SH is suggested. **E**

2.9 | Sick day management

- Brief and easy-to-understand visual education materials in the local language(s) on how to manage diabetes during intercurrent illnesses is suggested. **E**

TABLE 2 Modified levels of T1D care for LRS

Topic	Comprehensive care	Intermediate care	Minimum care
Choice of insulin	Regular insulin/rapid acting analog (bolus) + glargine (basaline)	Regular + NPH insulins	Regular + NPH insulins
No of times	1. Regular insulin/rapid acting analog before each meal + basal once or twice (morning and/or bedtime) 2. Regular insulinbefore each meal & rapid acting analog in school or for correction doses + basal once or twice (morning and/or bedtime).	1. Regular insulin before each meal + NPH at bedtime. 2. Regular insulin & NPH before breakfast and dinner + Regular insulin before lunch/ large snack	1. Regular insulin before each meal and NPH at bedtime. 2. Regular insulin & NPH before breakfast and dinner + Regular insulin before lunch/ large snack
Storage of insulin	In refrigerator	In refrigerator Earthen pot in case of power cuts	Earthen pot for insulin in regular use/ nearby fridge for stored supply.
Insulin syringe reuse	As little reuse as possible. Use of pen devices, specially in school and during travel.	Change after 3–6 times	Use for up to 10 times. Discard earlier if touched somewhere, blunted or painful.
Disposal of syringes, and other sharps	Collect in a puncture-proof bottle: give to hospital on visit. Recycle rest of plastic	Collect in puncture-proof bottle: give to hospital on visit.Recycle rest of plastic	Collect in puncture-proof bottle: give to hospital on visit.Recycle rest of plastic
Glucose monitoring	SMBG: Individualized pattern for 7–10 BGL, including 2–3 am, daily. Additional BGL for unexpected exercise, hypos, sick days. CGMS: constant use if possible, or intermittently HbA1c lab/ point of care every 3 months Tracking Time In Range	SMBG: Individualized pattern for 4 BGL daily; 7 BGL profile once or twice a week. Additional BGL for unexpected exercise, hypos, sick days. CGMS: once in 3–6 months for identifying hypoglycemia and understanding patterns. HbA1c point of care every 3–4 months.	SMBG: 7 BGL profile once or twice a week. Additional BGL for unexpected exercise, hypos, sick days. HbA1c whenever possible, preferably at least every 6 months
Screening	Height, Weight, growth charts, pubertal stage (>10y age), BP, injection sites, clinical examination in each visit for visual/ sensory changes.	Height, Weight, growth charts, pubertal stage (>10y age), BP, clinical exam in each visit for visual/ sensory changes	Height [marked on the wall], Weight, pubertal stage (>10y age), BP, clinical exam for visual/ sensory changes annually.
Diabetes care and education: by whom?	Treatment by specialist. Education by a team of educator, nutritionist, psychologist, can be by telemedicine if not available locally 24 × 7 helpline support. Coaches to train in basics T1D Leaders to motivate Periodic camps	Treatment by specialist. Education by a team of educator, nutritionist, psychologist via telemedicine Helpline support. Coaches to train in basics T1D Leaders to motivate	By the local doctor, in touch with specialist by telemedicine By training paramedical staff via short-term courses Using experienced PwD or caregivers as coaches.
Diabetes Education: how? (tools)	WhatsApp groups, educational videos and material, peer group activities, mobile apps Online sessions, handbooks & logbooks Displays in clinic: Audio/ video/ pictorial posters/ leaflets	WhatsApp groups, educational videos, peer group activities, mobile apps Online sessions, handbooks & logbooks Displays in clinic: Audio/ video/ pictorial posters/ leaflets	WA groups: audio messages and videos if phone (own or neighbour's) available Displays in clinic: Audio/ video/ pictorial posters/ leaflets Peer interaction: casual or structured Indigenous games and tools such as snakes and ladders to teach low literacy groups.
Diabetes Education: what?	Structured age- appropriate diabetes education. Emphasis on self-dose adjustment skills. Calculating insulin correction factor (ICF)	Structured age- appropriate diabetes education. Emphasis on self-dose adjustment skills. Dose adjustments as per sliding scale	For all: Insulin care, insulin mixing, hypoglycemia management, sick day management. SMBG: Understanding implications of the readings with basics of self-dose adjustments.
Nutrition	Ability to balance meals, carb counting, Calculating insulin carbohydrate ratio (ICR) Dose adjustment accordingly.	Balanced meals. Recognizing macronutrients. Food exchanges (with pictures) Approximate carbohydrate counting	Of the available local food: Concept of balanced plate and frequency of meals. Recognizing carbohydrates, proteins, fats and fiber. Approximate/ Visual Carb Counting can be learnt.
Frequency of visit to hospital	Once in 3 months if no problem. In communication with educator team online.	Once in 3 months if no problem. In communication with the educator team online.	Once in 2–3 months and in touch with coach frequently. Newly detected: 2–3 times a week for 2 weeks or longer to learn basics.

TABLE 2 (Continued)

Topic	Comprehensive care	Intermediate care	Minimum care
	For new families: Frequent (?daily) visit plan till basics of education taught, motivation given, can adjust doses and practice self-care.	For new families: Frequent visit plan till basics of education taught, motivation given, can adjust doses and practice self-care.	
Annual complication screening	Annual screening as per age and duration of diabetes [follow guidelines] Government or private facility depending on affordability.	Annual screening as per age and duration of diabetes [follow guidelines]. Refer to nearest government hospital or NGO.	Refer to nearest Government facility or NGO for annual screening Tests during NGO camps whenever possible.
Resources	Mostly or wholly out of pocket by PwD (may get partly through support). Form a group, negotiate for lower prices from companies. Reach out to various NGOs/ Clubs who run support programs.	Partly out of pocket by PwD and partly through support. Forma group, negotiate for lower prices from companies. Reach out to various NGOs/clubs who run support programs.	Reach out to NGOs, local politicians, regional or national Diabetes Associations, rich PwD with T2D/ T1D.
Exercise	Understand and plan different types of exercise. Check BGL to learn to adjust doses before, during and after exercise.	Understand and plan different types of exercise. Learn to adjust doses before, during and after exercise.	Local games with education for foot care & hypoglycemia Emphasize no exercise if food insecurity. Monitor if hypoglycemia.

- During an illness, frequent SMBG monitoring (3–4 hourly if possible), and, if available, blood or urine ketones 6–8 hourly is recommended. **A**
- When ketone testing is unavailable, medical care should be sought early. Insulin should not be stopped; hydration should be maintained with salty or sweet liquids based on BGL. **C**
- If glucometer/BGL strips or urine/blood ketone testing is not possible during sick days, urine glucose should be monitored to approximately assess the severity of hyperglycemia. **E**
- It is desirable for PwD in rural and remote areas to have close contact with their DCT during sick day management. **E**

2.10 | Diabetic ketoacidosis

- DKA may be more common in LRS, due to inadequate awareness, misinformation, and barriers to accessing care. **C**
- Mild and moderate uncomplicated DKA can be treated with subcutaneous (SC) Regular insulin (or rapid-acting insulin analogs, if available and affordable). This can be done at the nearest peripheral health set-up, with virtual consultations with an expert. **B**
- It is useful to provide written instruction sheets to families regarding the prevention and management of DKA, for health workers in rural and remote areas, where access to expert HCP is not available. **E**
- The incidence and severity of hypokalemia and hypoglycemia may be higher in malnourished PwD during DKA management. **C**

2.11 | Psychological care

- It is important to recognize psychosocial issues such as stigma, diabetes distress, eating disorders, anxiety and depression, family issues, attention deficit disorders, fear of hypoglycemia, alcohol and other substance abuse in PwD and their caregivers. **E**
- Inflexible treatment regimens, inadequate or inappropriate DSME, frequent complications such as recurrent DKA or excessive/ severe episodes of hypoglycemia, and financial distress worsen these conditions. **E**
- Psychological status is improved if all members of the DCT consistently use a positive tone and non-stigmatizing words, diabetes peer support, effective DSME, motivational interviewing and empowerment techniques. **E**
- Telemedicine may improve access to appropriate mental health support for PwD and caregivers. **E**

2.12 | Very young (preschool) child

- Diabetes management is more challenging in very young children and increases the parenting burden. **C**
- Early recognition of symptoms is paramount, as symptoms such as increased thirst or urinary output are easily missed. **C**
- DKA may be mistaken for other common illnesses such as gastroenteritis, respiratory infections, urinary infections, malaria, and parasitic infections. **C**
- MDI regimens with long-acting analogs for basal needs are suggested, depending on supply and affordability. **E**

- Frequent SMBG and CGM are desirable, based on availability and affordability. **E** Donors may be approached to provide supplies. **E**

2.13 | School

- Every PwD has the right to receive an education, wherever they live globally. **E**
- It is desirable that school staff are educated by parents and DCT members, either by outreach visits or virtual meetings; and the PwD supported, for safety and efficacy. **E**
- It is advisable for each PwD to have an individualized annually updated written Diabetes Management Plan (DMP). **E**
- It is strongly encouraged that school staff permit and supervise BGL testing, insulin administration, taking extra calories when needed, and other diabetes care activities. **E**
- It is desirable for school staff to know how to prevent and manage hypoglycemia, hyperglycemia, and other emergencies. **E**
- It is desirable that comprehensive legal protection for PwD is available, incorporating supervision of diabetes management at school, even in places without special laws. **E**

2.14 | Adolescence

- Adolescence and T1D may be a challenging combination especially in LRS, where social taboos, discrimination, financial constraints, lack of adequate medical facilities, and lack of expertise in managing adolescents further impede the delivery of care. **E**
- Psychosocial support is essential, by the DCT and by role models and peers, particularly for PwD living in remote areas. **E**
- It is desirable to proactively discuss the following issues related to adolescence with the PwD and their family: greater glycemic variability, need for more frequent SMBG, higher insulin requirements, screening for complications and associated increased costs. **E**
- It is desirable for DSME to be used at clinic, in group sessions, at diabetes meetings camps, together with peer support, to encourage and engage the PwD directly, and reduce isolation. **E**
- It is desirable to proactively and sensitively discuss topics such as menstruation, contraception, driving, smoking, alcohol, other substance abuse, and psychosocial co-morbidities such as illiteracy, attention deficit disorders, anxiety and depression in the PwD and their close family members. **E**

2.15 | Microvascular, macrovascular, other complications, and monitoring

- Baseline and regular screening for complications (as below) are essential and must be documented in the medical records annually, with interpretation, and reasons for omissions. **A** Screening can be facilitated with governments or NGOs to decrease or remove financial barriers. This allows prevention and early identification of micro- and macrovascular complications and is cost-effective in the long-term. **E**
- It is essential in all settings that growth is monitored and charted, as well as physical development and puberty. Height and weight should be plotted on standardized growth charts at every visit. **C**
- It is essential at every clinic visit that every PwD has a general physical examination, blood pressure (BP) measured using an appropriate sized cuff if possible, injection sites inspected and feet examined (for cracks and calluses). **C**
- Thyroid status should be monitored with TSH at diagnosis, then every 1–2 years, along with monitoring of growth, puberty, and goiter. In the absence of annual TSH screening, physical examination and specific thyroid related review become more important, with TSH testing essential for those with slow height velocity, delayed puberty, unexplained weight gain, constipation, or fatigue. **B**
- It is desirable that screening is performed for other comorbid conditions (such as CD) as needed, including specific documentation of possible symptoms, and laboratory investigations where available and affordable. **E**
- It is essential to screen for nephropathy, retinopathy, neuropathy, and dyslipidemia, especially if glycemic status is suboptimal, or if there is medical or family history of diabetes or other complications. **A** The frequency and extent of screening will depend on available resources and affordability.

2.16 | Fasting

- PwD in LRS may opt for fasting because of various reasons. **E**
- Fasting is permissible only if glycemic status is optimal, hypoglycemia awareness is present, frequent BGL monitoring is feasible, with willingness to break the fast without penalty when hypoglycemia, ketosis or dehydration occurs. **B**
- Insulin doses and schedules should be adjusted as per the rules and duration of the fast. **B**
- In religious fasting, all religious authorities recognize the need for 'not-fasting' if fasting would endanger the health of the PwD. This can be emphasized to the PwD and family to remove guilt. **E**

2.17 | Surgery

- Insulin must be administered to all persons with T1D during and after surgery, to avoid ketosis/DKA. **A**
- It is preferable to perform surgery in a facility that can accommodate administration of IV fluids, has at least minimal laboratory support, and has experienced staff available on site or with virtual consultations by HCP. **E**
- It is desirable to perform elective surgery when glycemia is optimal, but emergency surgery should not be delayed. **E**

2.18 | Type 2 diabetes

- T2D is increasing with the global obesity pandemic (LRS as well as middle and high resource settings), although some pre-disposed ethnic groups may be non-obese. **B**
- Socioeconomic status (SES) has large measurable associations with T2D. **B**
- Cultural, social, geographic, and economic barriers may prevent the implementation of behavioral change. These social determinants of health impact onset, prognosis and course of T2D, as well as obesity and the metabolic syndrome. It is desirable to prescribe lifestyle modification in the life context of the youth and family. **E**
- Treatment planning should consider household food security, household stability and family financial resources. **E**
- Metformin is the initial therapy of choice. **A** If HbA1c is >8.5% and ketones are present, long- or intermediate-acting insulin should be prescribed initially. **B**
- If islet autoantibody testing is not available, then family history, evidence of insulin resistance (acanthosis, skin tags) and the course of diabetes may provide clues to the diagnosis and whether long term insulin is needed. **E**
- Youth with T2D should be screened for hypertension, dyslipidemia, thyroid and liver dysfunction sleep apnea, and psychological comorbidities including learning difficulties, depression, anxiety, diabetes distress, and disordered eating, at diagnosis and on follow-up. **B**

2.19 | Language matters

- It is desirable that the DCT members educate the family to avoid use of stigmatizing words, which may promote negativity. These include, but are not limited to, words and phrases such as 'suffering from diabetes', 'sick child', 'diabetic child', 'other normal children', 'poor control'. Motivational interviewing techniques should be encouraged for all HCPs. **E**

3 | INTRODUCTION

In many parts of the world, especially south-east Asia, Africa and South America, T1D numbers seem low as many persons may be undiagnosed and untreated, or sub-optimally managed, with early mortality and frequent acute complications.[1–10] This situation seems to be improving, with better survival, but most of the available global T1D data is from developed countries, not from LRS. The T1D Index seeks to fill this void by assessing, using mathematical modeling, the probable numbers of persons with T1D and the decades of healthy life years lost to T1D.[11] Similarly, youth-onset T2D is also increasing, in parallel to the obesity epidemic.[12–16]

HCP in LRS may feel overwhelmed by best practice recommendations given in the international guidelines, which may not be possible to follow due to costs, limited availability of diabetes care supplies, trained personnel, community awareness and support, social stigma, and government policy recognition. However, it is desirable for them to follow these LRS guidelines, to provide best possible care given their local circumstances, while striving to improve the level of care (Table 2) when situations improve.

Economic constraints due to the high, recurring costs of diabetes care, and/or lack of government aid and/or insurance support put the onus of care on the family. Indirect costs such as travel to clinic, or taking leave from work, may further reduce families' ability to access care and supplies.[17] With costs usually paid out of pocket, the individual family's ability and willingness to spend determine quality of care.[18–20]

Societal conditions such as large families, taboos and discrimination, low literacy and low numeracy add further challenges. If disease, war, terrorism, or natural disasters occur, their impact on an already constrained situation is much more severe.

Resource constraints, poverty, and illiteracy (reading and numeracy) may also be present in regions of high-income countries (HIC), or resource constraints (war, natural disasters, etc.) may develop suddenly. Therefore, rather than discussing specific countries, these guidelines focus on what can be done in settings where there is variable, suboptimal access to diabetes care supplies (including insulin, monitoring systems, technologies) and trained personnel, and/or food insecurity and other constraints.

Depending on the resources available, the helpful concept of 'minimal, intermediate and comprehensive levels of care' has been adapted and used in this Chapter (Table 2).[21] This stratification can assist government policy makers, professional health planners, community advocates, and HCP.[22]

This guideline is not an endorsement of suboptimal care or commitment. Rather it discusses options and guidance to provide best possible care within whatever limited resources are available, while encouraging all families, HCP, communities, advocates, and governments to strive for the next level of care. The guiding principles are to encourage developmentally appropriate self-reliance and diabetes care, embedded in a relationship of trust and motivation between the HCP and the PwD and family.[23–26]

ISPAD strongly advocates and encourages:

- Optimization of diabetes management and ongoing, documented education, with the given resources, while striving for improvement in level of care,
- All communities to provide opportunities and avoid discrimination,
- Training of school personnel and other caregivers,
- Governments, medical agencies and insurance providers to facilitate care and prevention,
- Non-profit organizations and support groups to work for the cause of T1D.

In LRS, the PwD may have to seek care from 'diabetologists' familiar with adult T2D management, but not with growth and development; or pediatricians unfamiliar with diabetes care; or general

physicians, unfamiliar with pediatric diabetes care and pediatric issues.[27] The resultant increased risk of acute and early chronic complications, reduced schooling and socializing opportunities, and reduced ability to work and earn, inflict preventable suffering and individual and societal costs, as well as early death.[28]

Fortunately, expertise and awareness among HCP are increasing. In every country and region, more governmental organizations and NGOs are providing supplies and psychological support. ISPAD's own advocacy and educational efforts include worldwide easy online access to a host of teaching materials, including these ISPAD 2022 CPG, and links to resources from international organizations such as Life for a Child (LFAC), Changing Diabetes in Children (CDiC), Children with Diabetes (CWD), and several national bodies and NGOs.

4 | DIAGNOSIS, EPIDEMIOLOGY, MONOGENIC DIABETES

In geographical areas where the known incidence of T1D is low, the rate of DKA at presentation is higher, due to lack of awareness and delayed or misdiagnosis.[29] HCP, especially in the emergency rooms, should be aware of the need to test the BGL with a glucometer, and suspect diabetes in any unwell young person, especially if there is a history of weight loss, lethargy, thirst, excessive urination, ants at site of urination, abdominal pain, or persistent/ recurrent infections. If symptoms are suggestive of diabetes and blood glucose testing is not available, urine glucose testing should be performed where possible. In all youth with hyperglycemia and clear symptoms, the diagnosis of T1D should be strongly considered and insulin administered. Death from missed or delayed diagnosis may drastically decrease if this is done.

The proportion of T1D, T2D and other types of diabetes varies markedly between countries and ethnicities.[30–35] Measurement of islet autoantibodies, C-peptide or genetic tests may not be routinely available or affordable in many parts of the world, and need not be done for classical T1D. They may be useful in regions with a higher proportion of T2D, especially in adolescents with obesity, markers of insulin resistance, and/or strong family history. Often the clinical course also helps distinguish T1D from T2D.

Advantages of genetic testing, and scenarios which arouse suspicion of monogenic diabetes, are discussed in ISPAD 2022 CPG Chapter 4 on Monogenic Diabetes. Infants under 6 months with diabetes (Neonatal Diabetes, NDM) may especially benefit. It is useful to know that some academic centers around the world offer these genetic tests free or at a low cost.

5 | STAGES OF TYPE 1 DIABETES

Detection of Stages 1 and 2 (positive islet autoantibodies but presymptomatic) using extensive genetic and antibody testing of the PwD's family members or the general population, may not be feasible in LRS. If the diagnosis of T1D is evident clinically, antibody and C-peptide testing are not routinely indicated, unless opportunities to participate in an ongoing prevention trial are locally available.

However, early diagnosis of Stage 3 T1D (hyperglycemia) is useful to prevent DKA. Therefore, strategies which increase awareness of diabetes among HCP and communities improve the chances of earlier diagnosis, before DKA develops.[36,37] This may be easily possible in family members and near relatives. Reduction in incidence and severity of DKA means less hospitalization, reduced cerebral edema and other immediate morbidities of DKA, reduced parental anxiety, reduced long term morbidity, and minimal mortality.[38]

6 | DIABETES EDUCATION

The many (more than 100) daily tasks of self-management, including BGL testing, taking insulin injections appropriately as well as adjusting doses, managing food and physical activity levels, require proper knowledge of diabetes. This is feasible if DSME is imparted right from the beginning and reinforced consistently. DSME is needed not only for the family of the PwD but other caregivers (e.g., school teachers, sports coaches, nursery/ creche staff, friends' parents) as well. A person-centered, self-empowering approach should be encouraged.

Local beliefs, myths, and previous experiences (e.g., T2D or T1D in the family) influence the way parents and caregivers accept the diagnosis and management plan. An effective way to handle myths, as well as improve acceptance, is to introduce the newly diagnosed family to peers who understand diabetes well. Meeting others their own age and SES, who have experienced the initial trauma and are facing the same challenges, can markedly improve acceptance and hope. Many families in LRS rely on local/ alternative medicines/ therapies; it is common for them to explore these options in the search for a cure, and omit insulin. Clear explanations and peer support at diagnosis are desirable to avoid this catastrophe.

In each center, it is desirable to develop a culture- and age-appropriate basic structured program, with periodic review, using educational material in the language the family is comfortable with, Visual aids such as diagrams, pictures, comics, kids' diabetes education pamphlets/ booklets, and videos, are useful, especially for those who are illiterate. Many diabetes associations now have freely available/ downloadable tools. The Pink Panther Diabetes manual as well as Hanas' Diabetes Manual are also available in multiple language translations.[24,39,40]

A multidisciplinary DCT of pediatric endocrinologist, dietician, diabetes educator and mental health specialist, all familiar with pediatric diabetes, is not likely to be available in most LRS. The local physician is encouraged to provide all these aspects of care.[24,39,40] However, physicians with few PwD in their care, often cannot spare the time needed to learn, understand, and then teach pediatric, adolescent, and young adult diabetes care to individual families. Therefore, education can be supplemented, thanks to the widespread availability of mobile phones, by telemedicine. During the COVID pandemic, this became widely accepted globally, making it easier to access care from experts and improve training and education. The

primary pediatrician/ physician, particularly if living in a remote area with little or no access to quality diabetes care and education, can coordinate care with expert centers.

Interactive web-based resources, apps on smartphones, text messaging for information, are useful for young people, who are naturally attracted to technology.[41] With a sizable number of people searching online for health-related content,[42] such content is created by health professionals, lay persons, not-for-profit and commercial organizations.[43] The treating HCP is encouraged to verify content, ensuring it is culturally sensitive and appropriate to the family's literacy level.

Contact with self-help groups and/or local or international charitable organizations at diagnosis may help provide emotional, financial, and logistical support.[44] Support by experienced family members of PwD, or senior PwD peers can be helpful in the absence of a multidisciplinary DCT.[45,46] Training them further and using their help to spread DSME can be practical, feasible and effective.[44]

The level and content of diabetes education is ideally individualized based on:

- Age,
- Interest, level of motivation, family support,
- Stage of diabetes,
- Literacy, numeracy, language, culture,
- Maturity, learning pace, degree of independence and self-motivation,
- Availability of basic facilities (insulin, refrigeration, BGL monitoring strips, meters and batteries, lab tests),
- Extent to which technology is available.

Teaching also needs to change over time, as the child/young person matures (or for a while, rebels), or if situations change (changes in financial status of family, changes in the medical center, migration, connectivity, war, terrorism, local disasters).

It is important for the DCT to ensure that the family is able to access adequate supplies to optimize care. To fill affordability gaps, low-cost or donated Regular and NPH insulins (vs. analogs), delivery systems (e.g., vials and syringes vs. pens), and inexpensive glucometer/strips can be advised. The family may need guidance on where to buy supplies, and/or which organization to contact for support. When HCP prescribe expensive insulins or glucometers/BGL strips, this may force families to ration or miss insulin doses or BGL testing. Less frequent SMBG testing can be detrimental, particularly in the initial months when the PwD transitions from initial high insulin requirements to the honeymoon phase (with associated risk of hypoglycemia), and then to higher insulin requirements (leading to risk of DKA).

After the initial survival skills have been taught, the DCT/ educator must maintain daily/ frequent contact with the family (if required, by tele- or video-calling), to help with the initial diabetes education and management.

To sum up, appropriate DSME imparted at diagnosis and reinforced regularly, establishes and maintains positive self-empowering attitudes to diabetes care, while countering and overcoming myths and beliefs.

Regular follow up is best encouraged by making the clinic visit as useful and interesting as possible. It is wise for the DCT to show interest in the young person rather than focusing only on diabetes. It is useful to develop a specific clinic time for T1D families. The waiting area provides a good opportunity to introduce parents/ caregivers and PwD to one another, encouraging them to interact. This strengthens the support groups as well. Innovative ways to utilize waiting time with games and quizzes which impart diabetes education, can be encouraged. Funds may need to be arranged for families which cannot afford the travel to the clinic.

7 | INSULIN THERAPY

The goals of therapy for LRS are no different from well-resourced situations, although they are much more difficult to achieve because of the limitations discussed. While many compromises may be needed, some are unacceptable, for example, using premixed insulins and twice-daily dose regimens, because these older regimens are known to be associated with worse time in range (TIR), more DKA, and more frequent as well as more severe episodes of hypoglycemia.[47]

7.1 | Choice of insulin and insulin regimen

All children and adolescents with T1D should be started on MDI regimens, using the cheaper conventional (Regular and NPH) insulins (or analog insulins if affordable and available). Basal needs are usually approximately 40% of the total daily dose (TDD), and can be met by either NPH or glargine. The price of biosimilar glargine has become close to that of conventional insulins in recent years in many regions, making it a feasible alternative to NPH for governments or donor agencies to procure.[48] It is useful in reducing nocturnal hypoglycemia and improving HbA1c.[49] Bolus needs are the remainder of the TDD, and are met by Regular insulin in divided doses, given before each meal and large snack, that is, 3–4 times a day. This ensures that insulin cover is available whenever carbohydrates are consumed, and doses can be adjusted according to the pre-meal BGL, the amount of food available, the exercise planned or anticipated, and given when the food is available. MDI regimens enable flexibility in dosing and timing, reducing the adverse impact of variable meal timings, food insecurity, and variable physical activity. They lessen postprandial and nocturnal hypoglycemia and hyperglycemia, improve QoL and school activities, as well as enabling better study and work.[47] MDI regimens are practical because currently available needles are very fine, lessening pain and needle phobia.

7.2 | Examples of MDI regimens

1. NPH is given once daily (before dinner or at bedtime), with Regular Insulin given before breakfast, lunch, dinner and any large snack (such as a meal with substantial carbohydrates which most children eat at school). The PwD can take the school bolus dose one period before

the mealtime break, to ensure the 30–40 min gap needed before eating.

2. NPH is given twice daily: before breakfast and at night, while Regular nsulin is given before each major meal/ large snack, as above. NPH and Regular insulins can be mixed in the same syringe for the morning and night dose, reducing the number of pricks.

3. Glargine is given once daily (either morning or bedtime), with Regular insulin boluses, as above. Sometimes, glargine may have to be split into morning and bedtime doses, with mealtime Regular insulin boluses, based on BGL pattern review as well as history of hypoglycemia.

Premixed insulins and twice-daily dose regimens are still used in many LRS, but they are non-physiologic and are not recommended for T1D. When pre-mixed insulin is the only available insulin, it may be given briefly until Regular and NPH insulins are available. The TDD can be divided into before breakfast, before mid-day meal and before dinner doses. The use of pre-mixed insulins is associated with more frequent and severe hypoglycemia, more hyperglycemia and DKA, and general inflexibility with dietary as well as exercise or sick day needs.[47] This is further exacerbated by the limited ability for frequent BGL testing in LRS. In situations of food insecurity, severe hypoglycemia can occur. In some parts of the world, donors may provide only premixed insulin. Since the cost per unit of insulin of Regular Insulin, NPH and pre-mixed insulins is similar, donations of Regular and NPH insulins should be insisted upon.

Similarly, the older twice-daily split-mix regimen is also not appropriate for T1D as the mid-day meal does not get adequate insulin cover, resulting in afternoon and evening hyperglycemia. Post-breakfast hypoglycemia can occur, especially in school when the parents are not able to adequately monitor, and then this impairs the PwD's ability to study as well as play. The risk of post-dinner and nocturnal hypoglycemia is often high. With food insecurity, hypoglycemia may become dangerous as well as more frequent and produce possible insulin omission in an effort to reduce such episodes, rather than adjusting the dose or timing of insulin. These glycemic swings occur even with very strict discipline in food amounts, timing and exercise, which is usually impractical. The adverse impact is worsened by the limited capacity for SMBG in such situations.

The resultant increased glycemic variability, with symptomatic and asymptomatic glucose disruptions at home, overnight, in school, and during activity, is associated with worse short-term outcomes, and reduced QoL. Ultimately more long-term diabetes complications also occur.

Over the years, the prices of insulin have come down and availability has improved because of increased production, especially of biosimilars. The lower cost of biosimilars has made adequate insulin regimens more affordable. The choice of insulin and insulin regimens should be individualized, based on the PwD's:

- Age, lifestyle and routine,
- Affordability, motivation and family support,
- Food availability,
- General health and presence of other disorders,
- Ability for self-management,
- Hypoglycemia awareness.

Additional factors in LRS include:

- Consistent availability, and cost of insulin,
- Refrigeration issues, with uninterrupted supply of electricity,
- Access to SMBG/CGM,
- Food insecurity,
- Social and financial circumstances,
- Access to health insurance, government, NGO, or other institutional support.

Whichever insulins and regimens are chosen, support by comprehensive DSME, appropriate for the age, maturity, and individual needs of the PwD and family, is needed.[50] The chosen insulins must always be available in sufficient amounts, with consistent quality and type, and adequate cold chain maintenance. The requirements should be discussed and reviewed periodically with the family.

Since insulin vials and syringes are the cheapest option, they continue to be the most common method of insulin administration.[51] Hence education regarding appropriate syringes (U40 vs. U100, shortest needle length of 6 mm) and techniques for mixing Regular and NPH insulins is important. In some countries, conventional insulin vials are available in both concentrations - U40 (40 U per ml) and U100 (100 U per ml), which can be a source of error in dosing. Though U100 insulin causes less pain on injection, families and donor agencies may prefer U40 insulin for several reasons - if paying out-of-pocket (lesser cost per purchase), if lacking access to regular refrigeration (insulin used up sooner), or if 0.5 U increments needed, for example, for a small child. The U40 syringes have 1 U increments so 0.5 U can be given, cf. the 1 ml U100 syringes which have 2 U increments. The DCT should teach and reinforce matching the insulin vial with the corresponding insulin syringe. The syringes may be used 3–6 times if proper care and asepsis are maintained.

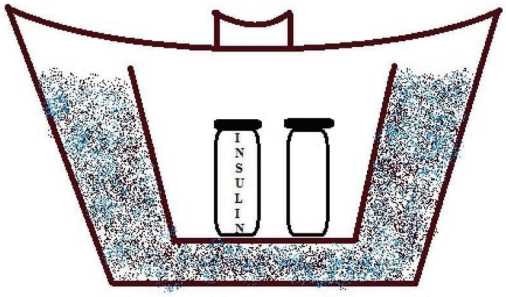
Dosing errors with pens tend to be fewer than with syringes, and pen needles of 4 mm length are available. Needles of 4 mm length are especially important in the very young and the under-nourished child.[52] Therefore, if available and affordable, insulin pens with 4 mm needles should be considered, especially if dosing or numeracy errors persist.

7.3 | Insulin storage

While insulin manufacturers' advice for storage of insulin is at 2–8°C, maintenance of cold chains may be challenging in LRS. Daily temperatures could reach as high as 45–48°C, which affects insulin stability. Insulin should be purchased from reliable pharmacies and carried home with a cooling arrangement. Insulin in use must be kept cool, preferably in a refrigerator, especially in the summer months.

Many families may lack access to regular refrigerators or electricity. In these situations, methods such as double-layer clay pots (Figure 1), goatskin, acrylate polymer bead wallets, and so forth. have

FIGURE 1 Clay pot (courtesy Dr Archana Sarda)



been devised to store insulin at temperatures below 25°C.[53] Kept in a shaded, airy place; they work well if humidity is low.[54,55] Alternatively, insulin can be transported and stored wrapped in plastic, in a thermos flask, along with 3–4 cubes of ice, which are replaced when they melt. Too much ice should be avoided.

Vials and cartridges of insulins are usually advised to be discarded after 4–6 weeks of opening as per the manufacturers' instructions. This may lead to significant insulin wastage. To avoid this, anecdotally many centers use insulins successfully for longer than 4–6 weeks. 'Older' insulin may sometimes have less potency and hence the insulin doses may need to be increased, as guided by SMBG. Subsequently, when a new insulin vial or cartridge is opened, doses can be reduced as necessary.[56–59]

7.4 | Sharps disposal

Diabetes care inevitably generates sharps - whether for insulin administration or SMBG. It is important that families are taught safe disposal. The discarded sharps are to be stored in a thick, puncture-proof plastic container with a tight-fitting lid, and carried to the health center or laboratory for safe disposal. It must be emphasized and reinforced that sharps must never be disposed of in the general garbage.[60]

8 | GLUCOSE MONITORING

8.1 SMBG It is crucial that treating physicians as well as families of PwD are aware that SMBG is an integral component of T1D management. Regular glucose monitoring, several times daily, whether using SMBG or CGM if available, is essential for effective management.[61,62]

Unfortunately, test strips and batteries are expensive and may be unavailable or unaffordable in LRS. Local and/or international NGOs increasingly assist with this. Lobbying to achieve favorable government, NGO, and insurance policies to make adequate (several times, every day) SMBG supplies available to all is important.

If availability of test strips is scarce, so rationing of testing is needed, it may be an option to check BGL a few days every week (for example every alternate or third day, or 2–3 consecutive days in a week). Keeping the meal and exercise pattern consistent throughout the week is helpful in these situations. Thus, if only 25–30 strips per month are available to the family, a 7-point BGL profile done once a week on a working/school day, can help discern patterns so that the doses/time/activity/diet can be planned accordingly on other days as well, with the guidance of the DCT. Monitoring on other days is then done as per individual need, for example, for unexpected exercise, or when hypoglycemia is suspected. One BGL test a day at different times is less helpful in guiding dose adjustments, though it may help in prevention of hypoglycemia. Performing a 6–8 point profile on the same day, as often as possible in a week, may be more useful.

PwD and their families are advised how crucial it is to maintain a record of the BGL, along with the food eaten and exercise undertaken. Analysis of these logs by the family themselves, discussed and documented in the health care records during each and every clinic visit, enables understanding and self-adjustment of insulin doses, food and activity, to improve management of diabetes and QoL.

It is common in all settings, for adolescents in particular, to enter falsified/ fabricated BGL. A non-judgemental, problem-solving approach to such situations may be helpful but awareness by HCP is key to such considerations. Motivational interviewing and empowerment skills frequently produce positive results and are helpful.

8.1 | 8.2 Continuous glucose monitoring

CGM has transformed diabetes care in recent years.[63,64] In many LRS, CGM is unavailable or simply unaffordable, as constant use may cost 3–10 times more than SMBG. However, availability may rapidly change. When comparing costs, while teaching the family or lobbying with policy makers, the savings on multiple BGL test strips, the reduction of acute and chronic complications, and the prevention of hospitalizations should be factored in, as it considerably reduces the cost

difference, while also reducing the pain of multiple daily pricks. The lifetime improvement of QoL, with fewer acute and chronic complications, must be emphasized by the DCT and communities lobbying for governments' (and NGOs') support in this regard. Regular CGM use reduced HbA1c by 0.98% even in LRS.[65] The technology is rapidly evolving, including opensource apps, which allow for calibration on smartphones, and improved accuracy. Where constant use cannot be afforded, intermittent use of CGM every few weeks may be considered. This can help the family understand the impact of different foods and activities on BGL. In addition, families may wish to use CGM during special situations such as travel, illness, exams, or pregnancy. Donors may be requested to help for special situations. It is desirable that the DCT keeps abreast of these and other technology changes and explore options with the PwD and families, open up discussions with NGOs and other potential donors as well as with health policy administrators.

9 | GLYCEMIC TARGETS

9.1 BLOOD GLUCOSE TARGETS Glycemic targets set by the DCT, especially the lower limit, will depend on many factors, including age of the PwD, family circumstances, frequency of BGL testing, access to technology, hypoglycemia awareness, and level of caregiver involvement. If the number of test strips is limited, advocating the lower BGL target as 80 or 90 mg/dl (4.4 or 5 mmol/L) may be more desirable than 70 mg/dl (4 mmol/L), in order to reduce hypoglycemia. For example, a rural family with poor literacy, able to afford only a few strips, and with little or no access to medical care in a crisis, or both working parents, may be advised to maintain BG above 90 mg/dl (5.5 mmol/L).

9.1 | The upper BGL target of 180 mg/dl (10 mmol/L) is suitable for most PwD in LRS.

9.1.1 | 9.2 HbA1c

HbA1c continues to have a central role in assessing overall glycemia, and provides useful insights, especially where SMBG is not frequent. Availability of point of care (POC) HbA1c measurements can be especially valuable in clinics in remote areas, as it can be offered in special camps. Limitations of HbA1c and POC testing must be kept in mind. Anemia, common in LRS, and hemoglobinopathies, may affect the result.

ISPAD continues to recommend a target HbA1c of <7.0% *without significant hypoglycemia*, in most cases, though this may be difficult to achieve in some LRS. If the risk or incidence of hypoglycemia is high, due to limited availability of supplies, the targets may be modified.

It is important to negotiate acceptable glycemic target ranges with the family, and then be consistent between all HCP looking after the PwD. These targets may be renegotiated when circumstances change, for example, if more test strips are available, or as the PwD matures and can become more autonomous.

HbA1c testing should be performed every 3 months, if available and affordable, with results discussed with the PwD and caregivers, and documented in the medical records.

10 | NUTRITION

Availability and affordability of food and the frequency of SMBG vary in LRS. Food insecurity adversely affects diabetes management,[66] and may be compounded by food inconsistency, inadequate SMBG, suboptimal DSME, and local suboptimal understanding, so the PwD may experience more frequent hypoglycemia and hyperglycemia, higher HbA1c levels, as well as nutritional deficiencies, including iron, calcium, protein and vitamin D. Regular monitoring and recording of growth (height, weight, BMI), plotted on standardized growth charts (and discussed with the PwD and family) enable detection of deceleration patterns, or growth rates inconsistent with mid-parental height, and perhaps help consider co-morbidities such as thyroid or celiac disease.[24,39,40]

Nutrient deficiencies will need to be assessed (e.g., Vitamin D deficiency due to several factors including inadequate sun exposure, or B12 deficiency in vegetarians/ vegans), and may necessitate supplements. Iron and folic acid deficiencies causing anemia are common in some regions; if local governments provide iron-folic-acid tablets in school, this is desirable for the PwD as well. Regular deworming may be needed according to the local protocols.

Local traditions, food culture, and food availability have to be assessed. Rather than providing fixed diet charts, practical modifications of pre-existing dietary patterns promote acceptance and psychological well-being.[67] The meals of a PwD are essentially healthy meals and the entire family should eat the same food. Some PwD in LRS live in close proximity with multiple relatives, sometimes sharing a kitchen. Those preparing food may be grandparents or older aunts and uncles; where possible, they are also encouraged to receive ongoing nutrition education either in clinic or with local group support formats.

Nutrition education starts with the basics of food composition and distribution. The plate method, with use of pictures (as in Figure 2), is an efficient tool to teach preparation of balanced meals as per local availability. The family is taught to include all macronutrients (complex carbohydrates, fiber, protein, and fat) and fluids in desirable proportions, with affordable options. Pictures can be sent to mobile phones, and are useful even for rural families with low SES and/or poor literacy, to teach inclusion of missing or inadequate macronutrients (often protein) in the right proportion and without excess carbohydrates (e.g., too much rice or potatoes).

If a dietician familiar with T1D is locally unavailable, nutrition advice can be supplemented by telemedicine and virtual educational tools. This must be added to the specific tasks of the physician or nurse and documented at least every 3–6 months in the medical records. Appropriate apps and educational material are available in many countries and languages, including the websites of LFAC, ISPAD, CWD and regional and national Diabetes Association websites, for visual carbohydrate counting.

FIGURE 2 Indian "thali" (plate), with balance of protein, fiber, carbohydrates, micronutrients. Half the plate has vegetables and fruits; quarter has complex carbohydrates, quarter has protein, with a side of low-fat dairy, and water as a drink. [Courtesy Dr Anju Virmani]

Junk foods[68] should be discouraged for the entire family (not just the PwD). Carbohydrate rich festive foods can be permitted as a treat on special occasions and celebrations, in small portions, with extra insulin and activity considered accordingly. Foods labeled 'diabetic', 'sugar-free', or 'fat-free' do not offer any advantage, are expensive, and should be discouraged.

The diagnosis of CD necessitates dietary counseling to ensure a gluten free diet (GFD). Home cooking becomes more important as ordinary commercial foods are likely to be contaminated with wheat, and gluten free foods are often more expensive. Fortunately, in most regions, millets and maize are cheaper than wheat and rice, so if the additional effort of eating home-cooked food with home-ground millets is put in, a GFD is affordable.

Meal plans will need periodic adaptations according to growth progression, pubertal changes, adiposity, activity, and alterations in lifestyle (e.g., moving to college, job or marriage); seasonal events such as harvest time; religious or national festivals; or change in the family circumstances or finances (e.g., one parent losing a job or the mother getting pregnant).

11 | EXERCISE

The WHO recommends 60 min of daily moderate to vigorous intensity physical activity (PA) for all children. Families may discourage PA because the PwD is perceived as being 'ill', and/ or due to fear of hypoglycemia.[69] They must be taught to manage PA safely, without hypoglycemia, by adjusting insulin doses and food intake, guided by SMBG. In some LRS, in crowded urban areas, or in unsafe regions, youth (especially girls) may be forbidden or unable to go out for active play. They can be encouraged to find alternative options indoors. On the other hand, the PwD may need to perform manual labor as part of the daily routine. Where manual labor is needed, stopping the PwD's participation accentuates the feeling of being different and a burden: PA can be encouraged with appropriate diabetes education and adjustments.

PwD in any setting must be encouraged to always use footwear, protective if possible, while exercising and playing, especially in poorly maintained streets or grounds. Regular foot self-examination and at clinic visits, and appropriate care of wounds, is encouraged.

12 | HYPOGLYCEMIA

The sharp reduction in incidence of SH seen with greater use of SMBG, MDI, insulin analogs, CGMS, and pumps, has not occurred in LRS.[70] Without optimal SMBG at home, school or work, the incidence and severity of hypoglycemia, especially nocturnal hypoglycemia, rise. Regular insulins are less physiologic vis-à-vis food and activity, and so increase such risks. SH can lead to cognitive impairment, especially in very young children, accidents and injuries, coma, convulsions, even death, including dead-in-bed syndrome. Nocturnal hypoglycemia is more difficult to detect and treat, and far more dangerous.

Therefore, hypoglycemia and fear of hypoglycemia continue to be major hurdles in trying to optimize glycemia, especially in LRS. The major contributors to hypoglycemia are suboptimal SMBG, non-physiologic insulin regimens (twice-daily split-mix regimens and premixed insulins[47]), errors in insulin administration, inadequate knowledge of insulin dose adjustments, food insecurity, unbalanced and/ or excessive PA, non-disclosure of diabetes due to social stigma, and unawareness about the honeymoon phase. Food insecurity (e.g., a fixed, prescribed dose of insulin has been given, but food is insufficient or unavailable; or nocturnal hypoglycemia if the PwD goes to bed hungry) may be associated with a feeling of shame, and not be mentioned by the family, unless specifically asked for. Such issues need proactive handling with care and sensitivity. Delay in having a meal may occur in many circumstances, not necessarily due to poverty, and should be discussed during clinic visits with specific documentation in the medical record.

Regular SMBG, including periodic 2–3 am BGL checking (or CGM if affordable and available), with adjustment of insulin doses, is key to preventing and treating hypoglycemia. The BGL diary should be discussed at each clinic visit and discussion documented. If conventional insulins are being used, education about resuspending NPH carefully, need for mid-meal and bedtime snacks, daily SMBG, and site rotation for insulin injections (avoiding lipohypertrophy) is regularly reinforced. If food insecurity is likely, education about insulin dose modifications, maintaining safety, and preventing hypoglycemia needs review and reinforcement. Checking overnight BG must be especially encouraged after excessive PA and reduced or delayed meals. In moderate

hypoglycemia, sublingual application of glucose or sugar appears to work better than oral administration.[25,71,72]

Management of SH can be particularly challenging in LRS, where glucagon is likely to be unavailable and/or unaffordable. When SH occurs, the PwD should be placed in a lateral position (to prevent aspiration), keeping the airway clear, and transferred immediately to the nearest healthcare facility for administration of 10% IV dextrose. Immediate access to health care facilities or trained personnel to detect and treat hypoglycemia may also be difficult, more so in remote areas. Anecdotally, a thick paste of glucose, sugar, honey, or other sugar source applied on the buccal mucosa, keeping the PwD in a lateral position, has been helpful many times. Innovations such as these, or keeping a cotton ball soaked in glucose/sugar solution in the buccal cavity, have saved many lives in LRS.

HCP in peripheral health settings may not be familiar with IV glucose administration. The DCT is encouraged to provide written documents for the family to give such HCP, giving simple, clear instructions for emergency management of hypoglycemia.

Availability of injectable glucagon should be strongly considered for donations by NGOs in addition to blood glucose meters, testing supplies and insulin. Newer injectable forms of glucagon no longer require refrigeration or premixing so that dosing is easier and less likely to be problematic or erroneous. Fear of using the older, glucagon "spear" needles is also avoided with these new formats. The newer nasal spray glucagon is easier to use, has more consistent BGL responses, minimal side effects and gives more confidence to the user for administration.[73] Consideration should be given for donations of nasal spray glucagon kits for home and school use if costs can be controlled, or covered by donations.

Whatever type of treatment for hypoglycemic emergencies is decided upon, initial education of the PwD and family members should be documented and routinely reinforced at least annually, as the PwD matures, assuming more self-care with less adult supervision as an adolescent and young adult.

13 | SICK DAY MANAGEMENT

DSME and simple written instructions for managing sick days at home; as well as for HCP in peripheral health settings; are important. Families are advised and reminded about the importance of 2–4 hourly SMBG and at least 6 hourly ketone checking if available and affordable, with maintenance of hydration with salty fluids, particularly in remote areas or where local health facilities are inadequate. Blood ketone testing is more reliable and can be encouraged when available for those in remote areas. If not feasible, urine ketone sticks should be made readily available, as they are inexpensive.

More widespread use of mobile phones has made it possible to send simple instructions in local language(s) or recorded message to caregivers, and enable them to contact the DCT quickly. Access to emergency contact numbers of DCT members is important, especially for families with low literacy. Education and reinforcement at least annually, with proper medical chart documentation by the DCT is important.

14 | DIABETIC KETOACIDOSIS

In LRS, DKA is likely to occur more frequently, particularly at diagnosis.[29] With infections predominating in LR scenarios, clinical mimics are gastroenteritis, respiratory infection, urinary tract infection, septicemia, acute malaria and other local infections. There may be areas with little or no emergency room or pathology support to make the diagnosis of DKA. In typical cases, the clinical features and presence of hyperglycemia (detected by high blood or urine glucose) and ketosis (urine or blood ketones) are sufficient to make the diagnosis of T1D in DKA, even if it is not possible to measure venous pH or serum bicarbonate. All HCP should know the key questions to ask relatives of extremely ill children, adolescents, or young adults, including any enuresis, nocturia, ants at the site of urination or unexplained weight loss. If the answers to such simple questions by HCP is yes, then there is an obvious need for an immediate finger stick BGL and/or urinalysis for glucose and ketone determination, where possible.[74] Delays in diagnosis lead to risk of and greater severity of DKA, more complications such as cerebral edema, and higher mortality of 3.4%–13.4% (due to sepsis, shock, renal failure etc.).[75] Further, minimal or no availability of IV fluids, venous access, medications, laboratory access, intensive care units and experienced HCP interfere with optimal treatment. Posters for increasing awareness of the general public (provided by youth with diabetes as volunteer distributors to schools, nursing offices, locker rooms, pharmacies and emergency facilities) can be adapted with local pictures and local language sources.[36,37,76] It is also important to increase awareness among primary care HCP to suspect and diagnose DKA early, provide initial emergency treatment, and know when to transfer to a more experienced health facility. Appropriate emergency telephone consultations should also be established, not only for specific medical questions that may arise, but also to facilitate possible transfers if necessary.

If serum pH or bicarbonate testing are unavailable, so that classifying the severity of DKA is not possible, this should not lead to delay in treatment. If available, families of PwD are advised to always have urine ketone strips (or better still, blood ketone meter and strips, if possible) and carry them to the health facility, if unavailable.

If IV fluid therapy is not available (no venous access, IV fluids or access to a cannula), small sips of a salty fluid or coconut water (since it is high in sodium) can be given as frequently as possible without causing vomiting. If the PwD is vomiting persistently, or too drowsy to drink, such fluids may be given by a nasogastric tube (at about 30% lower rate than calculated and increased as tolerated). In the drowsy person, the HCP should consider the balance between the risk of aspiration with the benefit of sustaining circulation.

If IV infusion pumps are not available and/or intensive monitoring is not possible, SC or IM insulin (Regular or rapid-acting insulin) injected every 4 or 2 h respectively may be advisable regardless of

DKA severity.[25,77] This is preferable to using an IV insulin infusion, which is difficult to precisely titrate. If IV fluid therapy is available but laboratory testing including electrolyte monitoring is not, standard rehydration fluids should be used, and potassium should be empirically added at 40 mEq/L once the PwD has voided. Dextrose 5%–10% should be added once the BGL approaches 300 mg/dl (17 mmol/L).

Clinical assessment of respiration, level of consciousness and cardiovascular status, and observation of fluid intake and output are achievable in almost all health care settings. If the number of BGL strips is limited, checks can be spread out, keeping initial tests further apart (as high BGL are expected), and saving test strips for later, as the BGL approaches 180 mg/dl (10 mmol/L).

15 | PSYCHOLOGICAL CARE

The constant stress of managing diabetes, with the added challenges of poverty, scarcity, insecurity, social discrimination, and cultural taboos can be overwhelming, leaving many families unable to cope. Diabetes care in LRS is often so focused on survival and access to medical supplies, that psychological well-being takes a back seat. Addressing psychological aspects is necessary to improve glycemia, QoL and outcomes.[78]

The first step is to sensitize the HCP and the caregivers that the mental health of the PwD and the caregivers matters. Families in LRS often report the PwD is being 'stubborn' or 'devious' or 'bad tempered', usually not recognizing these as psychological issues which need to be addressed. Families may resist seeking professional support, and indeed, it may not be available. It is important not to judge a family/ caregiver for either being a cause for the problem in the first place, or for being unwilling to prioritize psychological care even if needed and available. Motivational style interviewing and empowerment techniques used consistently by all members of the DCT have been shown to be extremely helpful in not only identifying such problems, but also in initiating discussions regarding medical as well as family and psychosocial issues with the PwD and family members.[40,50]

Diabetes may be considered stigmatizing, more so in LRS. In the absence of flexible insulin regimens or resources for adequate SMBG, the reduced flexibility of food choices and timings of meals and activity, and the constant fear of an embarrassing event due to hypoglycemia, often lead to anxiety and depression and can escalate to (secret) fear of hypoglycemia and omitting insulin and episodes of recurrent DKA. Repeated episodes of hypoglycemia and marked glycemic variability can cause tiredness and mood swings, which are interpreted as "bad behavior". This situation is worsened if the family considers diabetes burdensome or shameful, and insists on hiding it from outsiders, or sometimes even within the family. The PwD may feel guilty and isolated, often cannot test or take insulin or food in time, and so runs the risk of more hypoglycemia, more hyperglycemia, and multiple long-term complications. Some families may not have access to healthy food choices, or the culture may not be supportive of healthy eating. If not educated about carbohydrate counting, the PwD must manage diabetes with fixed meal plans, further accentuating the feeling of being different and abnormal.

Fortunately, many families in LR settings have strong family bonding and support, which can help cope emotionally and financially. Sometimes, the extended family itself may be a cause of stress, with interference in the management of T1D. Family support may also be absent in specific situations, for example, migrants, displaced or refugee families, those living in or escaping from conditions of war, terrorism, or other major social upheaval; or simply if both parents in a nuclear family have long working hours and so are unable to appropriately supervise the PwD. There may be barriers in language or cultural differences from the DCT. These factors, as in well-resourced settings, may lead to or worsen psychopathology, including depression, diabetes denial, eating disorders, fear of hypoglycemia, or recurrent DKA in the PwD. Family psychosocial problems may be aggravated by having to deal with a demanding chronic illness along with fears about the future health of the PwD. This can be a major impediment to achieving reasonable glycemic management and QoL. The situation is worsened if psychological health issues are also treated as taboo and stigmatizing; or if they are self-treated with alcohol, marijuana or other substance abuse.

Often these social and financial problems are much greater for girls and women with diabetes. The burden of caring for the PwD may be disproportionately placed on the mother. The DCT is encouraged to involve other family members in participating and taking ownership of the PwD's diabetes care and specifically consider inviting fathers to clinic sessions or education sessions, not just mothers; as well as considering invitations for older siblings of the PwD, friends and grandparents or other relatives who may be available and appropriate to receive not only education but also support from the DCT.

Mental health specialists familiar with T1D are often not available locally, but may be accessed virtually. In addition, contact with older, well-adjusted PwD or with PwD parents can provide support. For example, CWD has an on-line support system that offers the PwD an age-appropriate "friend" who also has T1D, and similarly can offer support for moms and dads as well as grandparents, as can local or national diabetes organizations and weekend or holiday or summer diabetes camping programs. Adolescents and young adults enrolled in colleges and universities also have such support programs available on-line.

16 | VERY YOUNG (PRESCHOOL) CHILDREN

Diabetes management, difficult at any age, is much more so in very young children. They have erratic eating, behavior and PA patterns, with little ability to communicate symptoms or understand. Recurrent hypoglycemia has the potential to cause permanent cognitive damage to the developing brain. Apart from acute complications, the risk of

chronic complications, as well as mortality, is higher. LRS pose additional challenges, since availability of insulin analogs, access to CGM or even frequent SMBG, adequate DSME, and trained HCP are likely to be insufficient.

Therefore, providing comprehensive DSME to the family at the onset is important. Telemedicine may help where trained personnel are not available locally. Parents of toddlers are usually younger, and may be financially and/ or emotionally insecure. Awareness about support with free or subsidized insulin, glucose strips, possible CGM, pathology support, and other needs can be helpful. It is essential that all members of the family are involved in diabetes care, with specific attention paid to inviting fathers and not only mothers to be fully educated and available for ongoing supervision and education. Other relatives, including grandparents and older siblings, who may be full or partial caregivers, should also be included at the time of initial diagnosis and in follow up sessions.

Most preschoolers in LRS remain on Regular and NPH insulin, administered by insulin syringes, as in the DCCT study. Insulin should be given before meals, not after. Administration of small doses is a practical challenge, as 0.5 U pens are expensive and usually unavailable. It is possible to give doses of U40 insulins with 0.5 U increments. If analog insulins are being used, 0.5 or 0.3 U insulin syringes should be used if available. Insulin analogs cost 3–4 times more, but may be preferred in case of repeated hypoglycemia, and may be affordable as the doses are small. Additional support from donors may be needed to help in such instances. Twice daily and premixed insulin regimens should not be used at all. Insulin syringes with the shortest needle length are needed.

Frequent SMBG (7–10 BGL daily) is crucial in this age group. There should be a high index of suspicion for hypoglycemia, especially nocturnal hypoglycemia. Use of CGM (continuous usage or once every few weeks) is desirable if feasible (perhaps with charity support).

A meal plan with a relatively consistent carbohydrate intake at meal and snack times, together with carbohydrate counting, is helpful, but often challenging. Tackling half-finished meals, erratic PA, and insulin dose adjustments should be taught and reinforced in a manner, which is understood. Sometimes giving preschoolers part of their mealtime insulin before and the remaining dose immediately after, can help to allow insulin adjustments for erratic eating, thus avoiding later hypoglycemia problems.

17 | SCHOOL

Resuming school following the demanding diagnosis of T1D can be challenging anywhere in the world. This may be exacerbated in LRS, where some families react to the diagnosis by taking the PwD (especially girls) out of school, because 'the child is sick', or for financial reasons. Many families or schools ask the PwD (more likely with girls) to conceal the diagnosis, which increases the psychological pressure as well as the risk of acute complications.

Sometimes, schools may refuse admission or continuation of schooling because of misapprehensions; usually due to lack of awareness of T1D or how it can be managed. Relevant diabetes education for caregivers in school and age-appropriate discussion with peers are helpful.[79–81] Schools may not have easy access to an HCP to deal with emergencies, either in-house or nearby, though access to mobile phones has greatly improved this. In LRS, the challenges may be exacerbated in varying degrees by other issues:

- Limited availability of insulin, often none of glucagon,
- Limited availability of BG testing supplies,
- Inadequate educational resources in local languages,
- Geographical distance and transport issues.

In hot weather, the insulin to be taken before the school meal/ snack (and glucagon if available) should be stored in a refrigerator, or in a cooling bag in the school bag, or in a double clay pot kept at an airy spot. The child should always carry a "hypo kit", containing a sugary drink, a snack to be given after correction of hypoglycemia, and a glucometer and strips in case BGL is not tested daily before taking insulin.

Each PwD should have an individualized DMP made jointly by the DCT, parents, and school staff. When mobile phones are available, they can be utilized for sending the DMP and other diabetes education material to the school staff, and maintaining contact between the PwD, staff, parents, and if needed, the DCT. During the COVID pandemic years, mobile phones and video-calls were extensively and effectively used.[82] Their continued use can help generate confidence in the parents and PwD, so that lost school days are minimized, especially in remote areas.

Parents should be made aware of legal rights as well as insights about the best way to handle diabetes with school staff. Pragmatism is necessary, as facilities may not be available or even feasible in some situations. Posters about diabetes symptoms available with local pictures and local languages can be freely provided to school administrators and nursing staff to help with local community awareness and decreasing stigma.[40]

18 | ADOLESCENCE

Adolescence is a difficult phase of life; the combination of adolescence with diabetes is particularly difficult, since the adolescent wants to fit in and not be different from his/her peers. Psychosocial, developmental, and sexual issues in adolescents and young adults with diabetes in LRS are similar to those in well-resourced settings. However, trained personnel to handle these issues are usually lacking, and there may be several additional challenges. Psychosocial health becomes difficult to focus upon by a family trying to make ends meet.[83] Many youth may have to start working early to supplement family income, while pursuing education/dropping out of studies, adversely impacting diabetes care.

In many cultures, girls face several restrictions, with the family's priorities being early marriage and pregnancy. It may be difficult or impossible to talk directly to or even examine the female adolescent because of social restrictions. In some cultures, taboos and secrecy around menstruation, sex education and substance use/ abuse make it difficult to detect or manage these situations. Stigmatization and discrimination may be more obvious. Families may resort to keeping diabetes secret, increasing diabetes distress, and complications. In very conservative families, adolescents, especially girls, may be given little freedom to think and act for themselves. If early marriage and pregnancy are a possibility, this should be acknowledged and planned, with pre-conception discussed with the PwD and family. Relevant religious, cultural, or societal issues can be asked for and addressed.[84] The myth that women cannot be pregnant because of diabetes must be removed[85] but the added risks of diabetes and pregnancy must be explained in an honest, compassionate manner, to help improve quality of life and also the health of the potential mother and fetus/ baby.

Psychological support through group education programs and support sessions once again are particularly valuable and cost-efficient in LRS. Residential camps or weekend sessions have been successful around the world, whatever the settings,[25,44] since adolescent needs and challenges are the same globally; more so in LRS lacking formal institutional support.

Risk-taking behavior by adolescents with diabetes also are the same globally. Education is vital to keep them safe. Physical or verbal abuse may occur, and referral to a mental health care specialist may not be possible: not available or refused by the family for fear of stigma. In these circumstances, the physician, nurse and/or dietician have to help as best as they can, with help from peers with diabetes, and telemedicine. Here, too, employing a motivational educational and empowerment approach and more frequent contact, visual or in person, according to availability of staff, can be extraordinarily helpful.

It is important that the DCT build a mutually trusting relationship with the PwD and caregivers, to reduce the chances of the young PwD being lost to follow up.

19 | TRANSITION

Across the world, transition to adult care is difficult. In many LRS, there may be no transition, as the same general physician or DCT sees children, adolescents, and adults. Where adult and pediatric care are separate, the pediatric team has to facilitate the transition as smoothly as possible. Some clinics in LRS transition at age 12 years while most transition between ages 15 and 21 years. There are numerous reports from around the world in high, middle and low resource settings that document the deterioration of glycemic control associated with increased acute and chronic morbidities in the PwD in the adolescent and young adult years,[86] and efforts to address these problems continue. Being aware of these difficulties, having honest discussions with the PwD and family and having joint programs for a few years between pediatricians and adult physicians has been helpful in raising awareness and addressing these issues.

20 | COMPLICATIONS AND SCREENING

Regular recording and tracking of height, weight, BP, and pubertal status just need care with measurement and record keeping: they cost nothing, while yielding considerable information. To be useful, these parameters must be accurately measured (e.g., ensuring proper instruments, correct technique, and for BP readings, appropriate-sized cuffs) and accurately recorded at least 1–2 times a year.

Height and weight, properly measured and plotted on standardized growth charts, with the mid-parental height (MPH) plotted on the right y-axis, are helpful, since children typically follow a centile more or less in consonance with the genetic endowment (accounted for by the MPH). Abnormal growth velocity can help recognition of abnormalities, can be shown to the parents also, and evaluated, so early treatment and correction can be provided. Decreased growth velocity and delayed puberty can occur with persistent dysglycemia, hypothyroidism, CD, other gastrointestinal causes, Addison's disease (hypoadrenalism), or chronic infections (such as hepatitis, chronic malaria, and parasitic infestations).[87] Dysglycemia can be due to several reasons: non-physiologic treatment plan, unaffordable insulin or expensive insulin analogs which are unaffordable (hence rationed or omitted), and/or with inadequate or no SMBG. Mauriac syndrome,[88] due to very severe longstanding dysglycemia, is characterized by growth failure, hepatomegaly with glycogenic hepatopathy, steatosis, and late pubertal development. Most examples of Mauriac Syndrome also have frequent significant psychosocial ramifications, family conflicts, and major problems with insulin and monitoring.

Similarly, BP and Tanner staging should be documented and commented upon at each visit. Physical examinations should be thorough, including simple tuning fork assessment of neuropathy. An in-clinic ophthalmoscope helps look for cataracts and early retinopathic changes, especially in those with longstanding high HbA1c levels, recurrent DKA, coexisting nephropathy, or neuropathy. Limited joint mobility (LJM) costs nothing to assess, and may allow the PwD to see an obvious change in their own body, which if present, is directly associated with increased neurologic, nephropathic and ophthalmic risks.[39,89] All this is especially valuable in LRS, where routine annual screening and testing for comorbidities may not be possible, so testing can be done at least for those with altered growth and development patterns as well as those with abnormal limited joint mobility.

Many NGOs e.g. LFAC and CDiC include not only HbA1c testing systems and supplies, but also on-site microalbuminuria testing systems so that at least these can demonstrate potential abnormalities on annual checkups. If abnormal, and certainly if progressively worsening, associated with higher HbA1c results, positive LJM findings and/or neuropathy or retinopathy by history or exam, warrant further specific renal function testing.

21 | FASTING DURING RELIGIOUS OBSERVANCES BY PEOPLE WITH DIABETES

Almost all religions advise fasting, with variable rules, for healthy adults, as a way of learning self-discipline, developing empathy for the

hungry, and gaining spiritual awareness. They also urge that fasting should not cause any harm to the person and forbid it under certain medical circumstances. For example, prepubertal children, menstruating, pregnant or breastfeeding women, individuals with acute or chronic illnesses whose health could deteriorate due to the fasting, those with an intellectual disability, or those who are traveling are exempt from Ramadan fasting as well as Yom Kippur fasting.

In fasts where water is not forbidden, the risk of dehydration is less, so more physical activity is permissible.

Before SMBG became prevalent, fasting was forbidden in T1D. With frequent SMBG, or CGM, fasting has become possible, but only if undertaken with great care, with intensive professional supervision. The exact pattern of dietary restrictions should be understood by the DCT, and pre-fasting counseling and education about insulin dose adjustments as necessary imparted to the PwD and family. They must understand the need for 6–8 BGL tests daily, and be willing to break the fast without penalty in case hypoglycemia or ketosis occur. PwD whose glycemia is not-in-target, who are unable or unwilling to monitor BGL frequently, or who need to perform physical labor, are at risk of severe hypoglycemia and/or dehydration, and should be advised not to fast, since self-harm is considered sinful. The desire to fast and conform with peers can be used as a reason to improve glycemia in the weeks preceding the fasting period and continued later.

Practicing Christians are expected to abstain from meat on Lent (from Ash Wednesday to Good Friday). A Daniel fast (no meat, dairy, alcohol, or oil allowed till sundown) would involve high carbohydrate intake, managed with carb counting and appropriate increased doses of pre-meal insulin. A Black fast (no food or water permitted till sunset) would need pre-meal insulin based on the carb count, for the pre-fast and post-sunset meals. Fasting rules for the Baha'is and for the Jews' Yom Kippur and Tisha B'Av (no food or water for 24 h) being similar to those during Ramadan, the same management can be recommended.

In the "Theravada or Hinayana" sect of Buddhism (mainly in Thailand, Lao, Myanmar, Cambodia, and Sri Lanka), novices, nuns and monks have breakfast and lunch before noon, but can drink juice or other sweet drink in the evening and before bedtime. This diet pattern of "8 precepts practice" is sometimes followed by teenagers or adults, and is easily managed by adjusting the basal-bolus regimen. The "Mahayana" sects' (Tibet, Bhutan, China, Taiwan, Korea and Japan) fasting consists of having the usual three meals a day of vegetarian food, milk, and egg: meat is forbidden. Regular insulin can be taken before each meal, the dose reduced as needed, based on carb counting as well as attention paid to no meat protein since that may also change the insulin dose required for that meal.

Hindu fasts are usually for 1 day, often with milk and/or fruits permitted. Longer fasts (e.g., 9 day fasts called *Navaratras*) permit use of millets and pseudo-cereals in place of cereals. Jain fasts can be for 8 days (*Aathai*), 3 days (*Tela*); or 2 days (*Chattha*), with no food, only water permitted till sunset: they can be managed as for Ramadan, but dehydration is not a concern. For *Ekashana*, only one meal is eaten till sunset; *Beyashna* means two meals only till sunset; in *Olee*, a specific additive, for example, ghee/ spices/ salt is abstained from for 9 days, thus altering glycemic patterns.

General principles to be followed for fasting are to reduce basal insulin by 30%–40% (if glargine, by reducing dose the previous night, or the same morning; if NPH, by skipping or reducing the morning dose and taking NPH only at night and again perhaps some reduction in dosage). The Regular insulin bolus is taken before any major meal, as above, with potential dose reductions and ongoing BG monitoring for safety reasons. Non-physiological regimens (two dose and/ or using premixed insulins) cause hypo- and hyperglycemia on an ongoing basis, and can be even more risky during fasting. If the PwD has been resisting the change to a basal bolus MDI regimen earlier, the desire to keep a fast could be used as a motivation to change well before the fast starts.

22 | SURGERY

Youth with T1D requiring major surgery should be referred to a center with sufficient resources to provide safe care, including facilities to measure blood gases, urea, electrolytes, and blood/ urine ketones; availability of bedside blood glucose meters; and healthcare staff experienced in pediatric/adolescent/young adult diabetes. Elective surgery should be performed with pre-existing glycemia optimized as much as possible. Basal insulin should be given to prevent DKA, with half the usual dose given before surgery. Rapid acting or Regular insulin can be given IV or SC, based on hourly BGL testing during and after the surgery, until the PwWD can accept food orally. Increased day and overnight blood glucose monitoring should serve as a guide to what IV fluids, foods and insulin doses are needed.

22.1 | Emergency surgery

In case of emergency surgery, when transfer to a better-equipped center is not possible, some alterations in care are possible.

If blood gases cannot be checked, urine ketones should be checked in freshly voided urine.

If general anesthesia is required, a temporary urinary catheter can be inserted, and removed post-surgery.

If testing urea and electrolytes is not possible, the HCP should carefully observe urine output and clinical signs for hydration status. Potassium is not advised if the individual has oliguria.

If a glucometer is not available, fresh urine samples should be checked for glucose monitoring, keeping in mind that the correlation of BGL and urine glucose is poor, and that hypoglycemia likely will be missed unless overtly symptomatic.

If no facilities are available for administration of IV fluids, then oral rehydration solutions can be used. The usual recommendation that no solid food should be given for at least 6 h before surgery holds good. Clear fluids and breast milk may be allowed up to 4 h before surgery (check with the anesthetist).

If DKA is present, the established treatment protocol for DKA should be followed, and surgery delayed, if possible, until circulating blood volume and electrolyte deficits are corrected. In the absence of DKA, IV fluids and insulin management should be commenced, as for elective surgery.

23 | TYPE 2 DIABETES

The prevalence of T2D in the young is rising in many parts of the developing world,[90] due to the epidemic of obesity, caused by increasing consumption of junk food, and decreasing PA. However, not all youths with T2D are obese, especially in Asia.[91] The risk of T2D rises if there are additional factors including low birth weight, rapid growth in infancy, and strong family history of gestational diabetes and T2D.

Adolescent girls are at particular risk in conservative societies: PA may be more curtailed, meals may contain more carbohydrates and less protein (which is expensive), less medical attention may be given, and the decision-making male members of the family may not be informed about "embarrassing" concerns such as irregular menstrual cycles.[91] Regular PA and reduction of junk food can be advised in all medical encounters with motivational interviewing and empowerment support as previously mentioned; and height, weight plotting and BP monitored regularly.

The rapid β-beta cell failure and the high morbidity seen in adolescent T2D underlines the need for prevention, early diagnosis, and aggressive treatment. The younger the child with T2D, the worse is the cardio-metabolic profile.[92] Therefore, prevention and early identification of obesity, and simple fasting and post-prandial BGL screening every 1–3 years, is especially important in LRS. Delay in diagnosis may result in presentation in DKA, which needs initial insulin treatment.

Distinguishing T1D from T2D is important. Often, parental and physician resistance to starting insulin results in oral medication advised to persons with T1D, resulting in chronic hyperglycemia, and acute and chronic complications. On the other hand, unnecessary insulin given to an adolescent with T2D can result in further weight gain. Testing for GAD and other autoantibodies to distinguish T1D from T2D or to diagnose "double diabetes" is often unaffordable. However, clinical behavior on follow up may give clues to distinguish the two conditions.

24 | SUMMARY

Diabetes care for LRS should be optimized by following general guidelines as much as possible. If optimized nutrition and activity cannot be arranged, educational efforts should address these issues adapted according to whatever possibilities exist. Advising near-physiological insulin regimens, optimizing SMBG, home analysis of BG results, adaptations for school (in school and after school activities), and sports participation as well as special celebrations involving food can all be done with appropriate education and at least annual updated reviews. The DCT should be consistent with advice, and document very specifically in the medical record, to avoid confusion. Education efforts should also be reviewed for changes with growth and development and any individual circumstances for the PWD and family. Monitoring growth, BP, sites, LJM, HbA1c, urine albumin excretion, and ophthalmologic, lipid, thyroid and any other examinations warranted by individual needs (e.g., testing for CD) to the extent possible and affordable, should be a priority. Preventing hypoglycemia and DKA, and handling mental well being, with motivational interviewing and empowerment efforts is needed on an ongoing basis. All these efforts, locally and via telemedicine, would help the PwD optimize health and QoL.

AUTHOR CONTRIBUTIONS

All authors contributed to writing of the Guidelines, and critically read and revised the manuscript.

CONFLICT OF INTEREST

Anju Virmani, Stuart J. Brink, Angela Middlehurst, Fauzia Mohsin, Franco Giraudo, Archana Sarda, Julia E. von Oettingen, Supawadee Likitmaskul, Luis Eduardo Calliari, Maria E Craig: none. Kuben Pillay has received speaker's honoraria from Abbott, Eli Lilly, Novo Nordisk and Sanofi in the last 3 years. Sana Ajmal receives support from *Meethi Zindagi* which is supported by Eli Lilly, Medtronic, and Roche. No financial support has been received.

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How to cite this article: Virmani A, Brink SJ, Middlehurst A, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Management of the child, adolescent, and young adult with diabetes in limited resource settings. *Pediatr Diabetes*. 2022;23(8):1529-1551. doi:10.1111/pedi.13456

APPENDIX A: ISPAD 2022 CLINICAL PRACTICE CONSENSUS GUIDELINES CHAPTERS LIST

Chapter numbers	Chapter titles
1	Definition, epidemiology, and classification of diabetes in children and adolescents
2	Stages of type 1 diabetes in children and adolescents
3	Type 2 diabetes in children and adolescents
4	The diagnosis and management of monogenic diabetes in children and adolescents
5	Management of cystic fibrosis-related diabetes in children and adolescents
6	Diabetes education in children and adolescents
7	The delivery of ambulatory diabetes care to children and adolescents with diabetes
8	Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes
9	Insulin treatment in children and adolescents with diabetes
10	Nutritional management in children and adolescents with diabetes
11	Assessment and management of hypoglycemia in children and adolescents with diabetes
12	Sick day management in children and adolescents with diabetes
13	Diabetic ketoacidosis and hyperglycemic hyperosmolar state
14	Exercise in children and adolescents with diabetes
15	Psychological care of children and adolescents with type 1 diabetes
16	Diabetes technologies: Glucose monitoring
17	Diabetes technologies: Insulin delivery
18	Microvascular and macrovascular complications in children and adolescents with diabetes
19	Other complications and associated conditions in children and adolescents with type 1 diabetes
20	Management of children and adolescents with diabetes requiring surgery
21	Diabetes in adolescence
22	Management and support of children and adolescents with diabetes in school
23	Managing diabetes in preschoolers
24	Ramadan and other religious fasting by young people with diabetes
25	Management of the child, adolescent, and young adult with diabetes in limited resource settings *This chapter*.