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Note to Readers

Overview

The *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* are intended to guide practice and are not intended to serve as a comprehensive text of diabetes management, nor are they intended to set criteria for research protocols. These guidelines are intended to inform general patterns of care. These guidelines are also intended to enhance diabetes prevention efforts in Canada and to reduce the burden of diabetes complications in people living with this disease.

As per the *Canadian Medical Association Handbook on Clinical Practice Guidelines* (Davis D, et al. Ottawa, ON: Canadian Medical Association; 2007), guidelines should not be used as a legal resource in malpractice cases as "their more general nature renders them insensitive to the particular circumstances of the individual cases." Health-care professionals must consider the needs, values and preferences of individual patients, use clinical judgement and work with available human and health-care service resources in their settings. These guidelines were developed using the best available evidence. It is incumbent upon health-care professionals to stay current in this rapidly changing field.

Unless otherwise specified, these guidelines pertain to the care of adults with diabetes. Two chapters — "Type 1 Diabetes in Children and Adolescents" and "Type 2 Diabetes in Children and Adolescents" — are included to highlight aspects of care that must be tailored to the pediatric population.

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Reproduction of the Guidelines

Website

These guidelines are available at http://www.guidelines.diabetes.ca.

2018 Clinical Practice Guidelines Expert Committee

The 2018 Expert Committee members were volunteers and received no remuneration or honoraria for their participation.

Each chapter was adapted from the 2013 iteration and we thank the previous authors for their insight and expertise.

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2018 Clinical Practice Guidelines

Introduction

Diabetes Canada Clinical Practice Guidelines Expert Committee

Robyn L. Houlden MD, FRCPC

Welcome to the *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*. Updated every five years, these comprehensive, evidence-based guidelines represent the sixth set since their introduction in 1992; and the first under the new name of Diabetes Canada. In 2017, the name of the Canadian Diabetes Association was changed to Diabetes Canada to reflect the seriousness of diabetes, and to increase perception of the organization as being committed to helping all Canadians with diabetes, as well as to ending the disease.

The Diabetes Canada Clinical Practice Guidelines are intended to guide practice; inform general patterns of care; enhance diabetes prevention efforts in Canada; and reduce the burden of diabetes complications. The intended users are all health-care professionals that are involved in the management of people with diabetes and those at risk of developing diabetes, with a particular focus on primary care or "usual care" providers. The guidelines are also intended for people living with diabetes. In this version, key messages directed at people living with this chronic disease have been added to each chapter.

For these 2018 Clinical Practice Guidelines, volunteer members of the Clinical Practice Guidelines Expert Committee have assessed the relevant peer reviewed evidence published since the last guidelines in 2013 through a rigorous systematic review process. They have then incorporated the evidence into revised diagnostic, prognostic and therapeutic recommendations for the care of Canadians living with diabetes, as well as recommendations to delay the onset of diabetes for at risk populations. The grading of all recommendations has been stringently reviewed by an Independent Methods Committee (see Methods chapter, p. S6).

The guidelines are meant to improve the quality of care and healthcare outcomes of Canadians living with diabetes. A primary purpose is to address clinical care gaps that exist, i.e. discrepancies between evidence-based knowledge and day-to-day clinical practice. The guidelines also summarize key research findings and make clinical decisions more transparent. They are meant to reduce inappropriate variation in practice, promote efficient use of health-care resources, empower people living with diabetes, identify gaps in knowledge, prioritize research activities, inform public policy, and support quality control activities, including audits of practice (1).

The guidelines represent a summary of material and do not provide in-depth background clinical knowledge which is typically covered more comprehensively in medical textbooks and review articles. They are not meant to provide a "menu-driven" or "cookbook" approach to diabetes care where the clinician has no discretion. In addition, they are unable to provide guidance in all circumstances and for all people with diabetes. People with diabetes are a diverse and heterogeneous group; treatment decisions must be individualized. Guidelines are meant to aid in decision making by providing recommendations that are informed by the best available evidence; however, therapeutic decisions are made at the level of the relationship between the health-care provider and the individual with diabetes. That relationship, along with the importance of clinical judgement, can never be replaced by guideline recommendations. Evidence-based guidelines try to weigh the benefit and harm of various treatments; however, patient preferences are not always included in clinical research and, as a result, patient values and preferences must be incorporated into clinical decision making (2). For some clinical decisions, strong evidence is available to inform these decisions, and these are reflected in the recommendations within these guidelines. However, there are many clinical situations where strong evidence is not currently available, or may never become available due to feasibility issues. In those situations, the consensus of expert opinions, informed by whatever evidence is available, is provided to help guide clinical decisions that need to be made at the level of the individual with diabetes. It is also important to note that clinical practice guidelines are not intended to be a legal resource in malpractice cases as their more general nature renders them insensitive to the particular circumstances of individual cases (1).

Key Changes

A number of changes have occurred with the development of the 2018 Clinical Practice Guidelines, including:

- Expansion of the Expert Committee to include 135 health-care professional volunteers from across Canada with broader representation from more allied health/interprofessional stakeholder groups. Expert Committee members bring expertise from

Conflict of interest statements can be found on page S5.

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diverse practice settings across the country and include professionals from family medicine, endocrinology, internal medicine, cardiology, neurology, nephrology, infectious disease, urology, psychiatry, psychology, obstetrics, ophthalmology, pediatrics, nursing, dietetics, pharmacy, chiropractics, exercise physiology and others.
- Inclusion and active participation of informed people with diabetes on the Expert Committee to ensure that their views and preferences inform the guideline development process and the recommendations, as well as development of key messages using lay terms directed at people living with diabetes.
- Increased recognition of ethnocultural diversity in Canada and its relationship with diabetes care.
- Increased involvement of Indigenous authors, organizations and health-care providers working with Indigenous populations and communities in the development of recommendations related to type 2 diabetes in Indigenous peoples. In addition, acknowledgment of the legacy of colonization and residential schools and their ongoing effects on Indigenous health, as well as the call to action of the 2015 Truth and Reconciliation Commission (3).
- Addition of new material on diabetes and driving, and post-transplant diabetes.
- More rigorous systematic review of literature with the assistance of the McMaster Evidence Review and Synthesis Centre; a former Evidence-based Practice Centre (EPC) designated by the U.S. Agency for Healthcare Research and Quality (AHRQ) under the auspices of their Evidence-based Practice Program which has completed high quality reviews for the Canadian Task Force on Preventive Health Care and the Public Health Agency of Canada.
- More rigorous review of the grading of recommendations by an Independent Methods Review (IMR) Committee. In the event of a discordance between author-assigned grade and IMR-assigned grade, the recommendation was arbitrated by an IMR co-chair.
- Wider external review by specialists, community primary care providers, academic Departments of Family Medicine across Canada, and specialty and disease support organizations.
- Additional efforts to manage and minimize conflict of interest among all Expert and Steering Committee members.
- Expanded harmonization of recommendations through collaboration with other organizations, including the Canadian Cardiovascular Society (CCS), Hypertension Canada, and the Canadian Cardiovascular Harmonization of National Guidelines Endeavour (C-CHANGE).
- Expanded dissemination and implementation strategies to support all recommendations with increased use of web-based technology.

A key message throughout the guidelines remains the importance of individualizing therapy for the person with diabetes. It is hoped that primary care providers and other health-care professionals who care for people with diabetes or those at risk of diabetes will continue to find the guidelines an indispensable resource. If properly applied, the guidelines should lead to improved quality of care, reduced morbidity and mortality from diabetes and its complications, and a better quality of life for Canadians living with this chronic disease.

The Challenge of Diabetes

The International Diabetes Federation (IDF) has identified diabetes as one of the largest global health emergencies of the 21st century (4). Each year, more and more people worldwide are diagnosed with this serious chronic condition with potentially devastating complications that affects all age groups. The World Health Organization estimates that, globally, high blood glucose is the third highest risk factor for premature mortality, after high blood pressure and tobacco use (5). In 2015, the IDF estimated that 415 million adults currently had diabetes and 318 million adults had impaired glucose tolerance, putting them at high risk of developing the disease in the future (4,6). Canada has also seen rising rates of diabetes. In 2015, the estimated prevalence of diabetes was 3.4 million or 9.3% of the population, and is predicted to rise to 5 million or 12.1% of the population by 2025, representing a 44% increase from 2015 to 2025 (6). The estimated prevalence of prediabetes in adults in Canada in 2015 was 5.7 million or 22.1% of the population (6).

Diabetes is the leading cause of blindness, end stage renal disease (ESRD) and non-traumatic amputation in Canadian adults (see Retinopathy chapter, p. S210; Neuropathy chapter, p. S217; Foot Care chapter, p. S222). Cardiovascular disease (CVD) remains the leading cause of death in individuals with diabetes and occurs two- to four-fold more often than in people without diabetes (see Cardiovascular Protection in People with Diabetes chapter, p. S162; Screening for the Presence of Cardiovascular Disease chapter, p. S170). People with diabetes are over 3 times more likely to be hospitalized with CVD, 12 times more likely to be hospitalized with ESRD and over 20 times more likely to be hospitalized for a non-traumatic lower limb amputation compared to the general population (7). Diabetes complications are also associated with premature death and it is estimated that 1 of 10 deaths in Canadian adults was attributable to diabetes in 2008/09 (7). Thirty per cent of people with diabetes have clinically relevant depressive symptoms (8); and individuals with depression have an approximately 60% increased risk of developing type 2 diabetes (9) (see Diabetes and Mental Health chapter, p. S130).

Diabetes and its complications increase costs and service pressures on Canada's publicly funded health-care system. This is because of an increased use of health services, loss of productivity and the long-term support needed to manage diabetes-related complications. Among adults aged 20 to 49 years, those with diabetes were 2 times more likely to see a family physician and 2 to 3 times more likely to see a specialist (3). Also, people with diabetes were 3 times more likely to require hospital admission in the preceding year with longer lengths of stay (2) (see In-Hospital Management of Diabetes chapter, p. S115). Canada has been identified as the country with the seventh highest spending on diabetes-related health expenditure, totaling 17 billion US dollars in 2015 (4). With the aging of Canada's population, the total direct health-care costs associated with diabetes are expected to continue to increase (10).

Prevention of Diabetes

Prevention of type 1 diabetes has not yet been successful, but remains an active area of research (see Reducing the Risk of Developing Diabetes chapter, p. S20). However, there is good evidence that the onset of type 2 diabetes can be delayed or prevented through a number of strategies, including healthy behaviour interventions (physical activity, weight loss), certain dietary patterns and pharmacotherapy (see Reducing the Risk of Developing Diabetes chapter, p. S20). An obesity epidemic is currently paralleling the diabetes epidemic worldwide (see Weight Management in Diabetes chapter, p. S124) with over 60% of Canadian adults and close to one-third (31.5%) of children and adolescents having overweight or obesity (11,12). There is an urgent need for governments to develop and evaluate strategies to prevent and treat rising rates of obesity and promote physical activity and reduction of sedentary time (see Physical Activity and Diabetes chapter, p. S54). In addition, Canada's diverse population, with some ethnic groups disproportionately

affected by diabetes, requires that health promotion and disease prevention and management strategies be culturally appropriate and tailored to specific populations (see Self-Management Education and Support chapter, p. S36; Organization of Care chapter, p. S27).

It is becoming increasingly apparent that social determinants of health play an important role in risk of diabetes and its complications. Two large public health surveys, the Canadian Community Health Survey (CCHS) (13) and the National Population Health Survey (14) have found that lower-income people are significantly more likely to develop diabetes. In the CCHS, the prevalence of type 2 diabetes in the lowest income group was 4.14 times higher than in the highest income group (13); and, in the National Population Health Survey, being in the low income group was associated with a 77% higher risk of developing type 2 diabetes (hazard ratio 1.77, 95% confidence interval 1.48–2.12) (14). The primary goals of public health interventions to prevent type 2 diabetes include the maintenance of a healthy body weight, physical activity and healthy eating (see Nutrition Therapy chapter, p. S64; Physical Activity and Diabetes chapter, p. S54); however, an individual's ability to adopt these healthy behaviours is influenced by many factors, including the social, environmental, cultural and economic conditions in which the individual lives (the "determinants of health"). These include income, education and literacy; employment and working conditions; food security; environment and housing; early childhood development; social support and connectedness; and access to health care (15) (see Type 1 Diabetes in Children and Adolescents chapter, p. S234). There is a need for governments to develop policies aimed at addressing poverty and other systemic barriers to health care (16).

Ethnocultural Diversity

Canada is a country rich in ethnocultural diversity. Canada boasts the highest percentage of foreign-born citizens than any other G8 country. More than 200 ethnic origins were reported in Canada in the 2011 census, with the most common ethnic origins with populations in excess of 1 million from highest to lowest, including Canadian, English, French, Scottish, Irish, German, Italian, Chinese, Indigenous, Ukrainian, East Indian, Dutch and Polish. The largest visible minority groups in 2011—South Asians, Chinese and Blacks (accounting for 61.3% of the total visible minority population)—are populations identified as being at high risk for diabetes; and were followed by Filipinos, Latin Americans, Arabs, Southeast Asians, West Asians, Koreans and Japanese (17). Studies have shown that culturally appropriate diabetes education (incorporating cultural or faith traditions, values and beliefs, delivery in the person's preferred language, adapted cultural dietary advice, the person's needs, and/or involving family members) results in improvements in diabetes-related knowledge, self-management behaviours and clinical outcomes (18,19) (see Self-Management Education and Support chapter, p. S36; see Nutrition Therapy chapter, p. S64). Given our diversity, Canada has much to teach the world of the importance of incorporating cultural traditions and health-care beliefs in diabetes care with many innovative models of diabetes health-care delivery. As Canada's Prime Minister Justin Trudeau has aptly stated "Diversity is Canada's strength" (20).

Diabetes rates are 3 to 5 times higher in Indigenous populations in Canada (7), a situation compounded by barriers to care for many Indigenous peoples. Indeed, the vastness of Canada poses challenges in providing comprehensive and uniform diabetes care throughout the country. Indigenous people are generally diagnosed at a younger age than non-Indigenous people (21), and Indigenous women experience higher rates of gestational diabetes than non-Indigenous women (22). Complications of diabetes are also more frequently seen among the Indigenous population than in the non-Indigenous population (23). The chapter on type 2 diabetes and Indigenous peoples in these guidelines (see Type 2 Diabetes and Indigenous Peoples chapter, p. S296) provides an important lens for recognizing the diabetes epidemic and challenges in providing diabetes care in these populations, and acknowledges the legacy of colonization and residential schools and their ongoing effects on Indigenous health, as well as the call to action of the 2015 Truth and Reconciliation Commission (3).

Optimal Care of Diabetes

Effective diabetes care should be delivered within the framework of the Chronic Care Model and centred around the individual who is practicing, and supported in, self-management (see Organization of Care chapter, p. S27). To achieve this, an interprofessional team with the appropriate expertise is required, and the system needs to support and allow for sharing and collaboration between primary care and specialist care, as needed. A multifactorial approach utilizing an interprofessional team addressing healthy behaviours, glycemic control, blood pressure control, lipid management and cardiovascular protection measures has been shown to effectively and dramatically lower the risk of development and progression of serious complications for individuals with diabetes (24–27) (see Cardiovascular Protection in People with Diabetes chapter, p. S162; Dyslipidemia chapter, p. S178; Treatment of Hypertension chapter, p. S186; Nutrition Therapy chapter, p. S64; Physical Activity and Diabetes chapter, p. S54; Pharmacologic Glycemic Management of Type 2 Diabetes, p. S88, Targets for Glycemic Control chapter, p. S42). In addition, individuals with diabetes must be supported in the skills of self-management since their involvement in disease management is absolutely necessary for success (see Self-Management Education and Support chapter, p. S36). People with diabetes require training in goal setting, problem solving and health monitoring, all of which are critical components of self-management. They also need access to a broad range of tools, including medications, devices and supplies to help them achieve the recommended blood glucose, lipid and blood pressure targets. Health outcomes depend on managing the disease effectively, and, without access to the necessary tools and strategies, Canadians living with diabetes will not be able to achieve optimal results. All levels of government should commit to investing in chronic care management and support the tools needed for successful self-management to ensure that optimal care can be delivered.

The Diabetes Charter

The Diabetes Charter for Canada clearly outlines the support Canadians with diabetes need to live to their full potential. It defines the right of people with diabetes to information, education and care that take into account a person's culture and language (see Appendix 1. Diabetes Charter, p. S307). The Charter also puts forth the right of people with diabetes to high quality care regardless of where they live. The Charter notes that governments have a responsibility to address the unique needs and disparities in care and outcomes of vulnerable populations who experience higher rates of diabetes and complications and/or significant barriers to diabetes care and support. These supports will help Canadians with diabetes manage their disease and related complications.

Other Topics

Each set of Diabetes Canada Clinical Practice Guidelines has become increasingly longer. This set of guidelines has seen the addition of material on diabetes and driving, post-transplant diabetes

and many other topics. However, it is recognized that several topics are still not covered. Oral health is one such topic. Gingivitis, an inflammatory condition of the gums surrounding the teeth, and periodontitis, the destruction of the ligament, bone and soft tissues that support the teeth, are two of the most serious dental conditions identified in individuals with both type 1 and type 2 diabetes (28). One study found that adults with poorly controlled diabetes had a significantly higher prevalence of severe periodontitis than those without diabetes (odds ratio 2.90, 95% confidence interval 1.40–6.03) (29). The pain, discomfort and eventual tooth loss associated with these conditions can lead to poor diet, nutritional deficiencies, psychosocial problems and an overall decline in quality of life. Periodontal disease may also increase the risk of developing type 2 diabetes because the body's inflammatory response to the periodontal bacteria may contribute to insulin resistance (30). In addition to gingivitis and periodontitis, individuals with diabetes have higher rates of dental caries and salivary dysfunction. The IDF has prepared guidelines on oral health for people with diabetes (31). The recommendations include: people with diabetes should see a dental professional regularly for oral health check-ups; health-care providers should enquire at least annually for symptoms of gum disease (including bleeding when brushing teeth, and gums which are swollen or red); and people with diabetes should be reminded that daily dental care is a normal part of diabetes self-management.

The relationship between diabetes and cancer is another topic not reviewed in this set of guidelines. Diabetes has been consistently associated with increased risk of several of the more common cancers (32); however, it remains unclear whether the association is direct (e.g. due to hyperglycemia), whether diabetes is a marker of underlying biologic factors that alter cancer risk (e.g. insulin resistance and hyperinsulinemia), or whether the cancer-diabetes association is indirect and due to common risk factors, such as obesity (33). It is also not known whether diabetes treatments influence risk of cancer or cancer prognosis. Pending further research, people with diabetes should be encouraged to undergo appropriate cancer screenings as recommended for all people in their age group and sex (33).

Conflict of Interest

The *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* have been developed by a multidisciplinary panel of volunteer experts and informed individuals living with diabetes based on a rigorous systematic review that rates the quality of evidence and strength of recommendations (see Methods chapter, p. S6). The need to incorporate patient preferences is also discussed throughout the document. Any discussion regarding off-label use of drugs includes the caveat that the use is off-label.

An explicit and transparent process has been used to minimize biases. Experts have not received honoraria or stipends. In addition, a policy defining manageable or disqualifying conflict of interest is strictly adhered to and available on request. Detailed conflict of interest statements using the International Committee of Medical Journal Editors (ICJME) disclosure form (http://www.icmje.org/) (with the addition of government funding sources) for all members of the Expert, Steering and Executive Committees, as well as the Independent Methods Review Committee, are posted publically on the guidelines website and updated annually for each year of the guideline development process (http://guidelines.diabetes.ca).

Research

Since Banting and Best's discovery of insulin in Toronto in 1921, the scope of diabetes research in Canada has been vast and the numerous studies both varied and unique. There have been huge strides and key advances in mapping and understanding the physiology, biochemistry and genetics of diabetes, as well as developments in the prevention, treatment and management of the disease. Key goals remain a desire to improve the quality of life of people living with diabetes and to find a cure.

Regulatory agencies should not apply these guidelines in a rigid way with regard to clinical research in diabetes. It is suggested that study protocols may include guideline recommendations, but individual decisions belong in the domain of the patient-physician relationship. The merits of each research study must be assessed individually so as to not block or restrict the pursuit of new information. Diabetes Canada welcomes the opportunity to work with regulatory agencies to enhance research in Canada and, ultimately, to improve the care of people with diabetes.

Cost Considerations

These clinical practice guidelines, like those published before, have purposefully not taken into account cost effectiveness in the evaluation of the evidence surrounding best practice for a variety of reasons, including the paucity of cost-effectiveness analyses using Canadian data; the difficulty in truly accounting for all relevant diabetes-related costs; as well as lack of expertise and resources to perform the appropriate cost-effectiveness analyses needed for all the clinical questions within the clinical practice guidelines. In addition, it is often difficult to philosophically judge which is of greater importance: clinical benefit for the person living with diabetes or cost to the health-care system, as well as, at what level of cost effectiveness should one consider a therapy worth recommending? Based on issues of feasibility and philosophical considerations of our role as recommendation developers, it was decided that cost would not be included in the recommendations to ensure that they reflect the best available clinical evidence for the individual with diabetes.

Dissemination and Implementation

Dissemination & Implementation Committee co-chairs and volunteer members were appointed at the beginning of the guidelines process. On an ongoing basis, the committee develops strategies to increase health-care practitioner implementation of the recommendations with the goal of improving health care for the person with diabetes. A major activity of the committee has been the development and maintenance of a guidelines website (http://guidelines.diabetes.ca/) which hosts the full guidelines; interim updates; a quick reference guide; key messages; health-care provider tools, slide kits, videos and webinars; as well as resources for people with diabetes and their support systems in a variety of languages. Both IOS and Android apps have also been developed.

Conclusions

Diabetes is a common condition with significant implications for quality of life, as well as mental health and physical conditions. Although there have been a number of advances in prevention and treatment, many individuals with diabetes have less than optimal glycemic control and are at risk for or have complications. Given the large number of people at risk for or currently living with diabetes, as well as predictions for dramatic increases in these numbers in the future, there is a need to improve prevention and treatment strategies, particularly for vulnerable and high

risk populations. Diabetes is also a complicated disease with a constantly expanding literature on new therapies and technologies that makes it challenging for health-care providers who care for people with or at risk for diabetes to remain up to date. These guidelines are a celebration of the work, contributions and creativity of health-care providers and people living with diabetes across Canada and contain evidence-based recommendations that provide a useful reference tool to help health-care providers translate the best available evidence into clinical practice as well as for people with diabetes and at risk of diabetes to make informed choices. It is hoped that these guidelines will also continue to provide all levels of government with the evidence they need when rationalizing access to health care so that the potentially beneficial health outcomes are maximized for people living with diabetes. Finally, Canada has much to teach the globe about optimal diabetes care through our world class research and innovative models of health-care delivery to Canada's rich ethnoculturally diverse population. We truly have much to celebrate.

Relevant Appendix

Appendix 1. Diabetes Canada Diabetes Charter

Author Disclosures

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2018 Clinical Practice Guidelines

Methods

Diabetes Canada Clinical Practice Guidelines Expert Committee

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Process

Following the process used to develop previous Diabetes Canada Clinical Practice Guidelines (1), an Executive Committee, Steering Committee and Expert Committee with broad expertise and geographic representation were assembled. In total, 135 volunteers, from diverse practice settings across the country, including professionals from family medicine, endocrinology, internal medicine, cardiology, neurology, nephrology, infectious disease, urology, psychiatry, psychology, obstetrics, ophthalmology, pediatrics, nursing, dietetics, pharmacy, chiropractic, exercise physiology, and others, participated in the guideline development process.

To further support the principles previously adopted to develop evidence-based recommendations, the current iteration of the guidelines engaged the McMaster Evidence Review and Synthesis Centre to systematically search, review and perform a critical appraisal of the literature. An online database (2) was used to enhance within and across chapter communication and documentation of the review of the literature, and to create guideline "memory" for future iterations of Diabetes Canada Clinical Practice Guidelines. Elements covered by the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument were incorporated into the guideline development process (3).

- Each recommendation had to address a clinically important question related to 1 or more of the following: detection, prognosis, prevention or management of diabetes and its sequelae. Health benefits, risks and side effects of interventions were considered in formulating the recommendations. Patient preferences and values were sought from expert panel members living with diabetes and the literature (where available).
- Whenever possible, each recommendation had to be justified by the strongest clinically relevant, empirical evidence that could be identified; the citation(s) reporting this evidence had to be noted adjacent to the relevant guideline.
- The strength of this evidence, based on prespecified criteria from the epidemiologic literature and other guidelines processes, had to be noted (4–9).
- Each recommendation had to be assigned a grade based on the available evidence, its methodological strength and its applicability to the Canadian population.
- Each recommendation was reviewed by an Independent Methods Review member and had to be approved by the Steering Committee and Executive Committee, with 100% consensus.
- Guidelines based on biological or mechanistic reasoning, expert opinion or consensus had to be explicitly identified and graded as such; harmonization was sought with other Canadian guideline bodies, including the Canadian Cardiovascular Society (CCS), Hypertension Canada and the Canadian Cardiovascular Harmonization of National Guidelines Endeavour (C-CHANGE).

Identifying and Appraising the Evidence

> *"The trials we have comprise islands of evidence, linked by shorter and longer bridges of extrapolation spanning oceans of uncertainty. . . The longer the bridge and the farther we are from an island, the shakier the extrapolation. . .*
> *More good outcomes trials means more islands, shorter bridges and less uncertainty. . .*
> *But there will always be an ocean to span and a bridge to cross." (Hertzel Gerstein, 2015)*

Authors for each chapter were assembled based on their relevant fields of expertise. Each chapter had 1 lead author, 1 or 2 "evidence resource" persons trained or experienced in clinical epidemiology or clinical research methodology, and up to 6 additional authors, as needed. At the outset of the process, committee members from each section of the guidelines attended a workshop on evidence-based practice and guideline development, in order to ensure a consistent approach to the development of recommendations. Committee members identified clinically important questions related to diagnosis, prognosis, prevention and treatment of diabetes and its complications, which were used as a basis for our literature search strategy (outlined below).

Authors were to explicitly define: a) the population to which the question would apply; b) the test, risk factor or intervention being addressed; c) an appropriate reference standard or control population to which the test, intervention or exposure was to be compared; and d) the clinically relevant outcomes being targeted. This information was used to develop specific, clinically relevant questions that were the focus of literature searches. For each question, strategies were developed combining diabetes terms with methodological terms. Two health sciences librarians with expertise in evidence-based practice constructed and peer-reviewed comprehensive searches of the relevant English-language, published, peer-reviewed literature using validated search strategies of electronic databases (MEDLINE, EMBASE, CINAHL, the Cochrane

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Central Register of Trials, and PsycINFO [where appropriate]). For topics that were covered in the 2013 Clinical Practice Guidelines, the literature searches focused on new evidence published since those guidelines, including literature published in September 2013 or later. For new topics, the search time frame included the literature published since 1990 or earlier where relevant. Updated literature searches were performed at two other intervals throughout the development process.

Once citation duplicates were removed, all references and full-text documents were loaded into DistillerSR (2). Using a priori defined criteria of inclusion and exclusion, all citations were screened at the title and abstract level in duplicate by team members from the evidence centre; full-text screening was completed by a diabetes clinician and methodologist for relevance. All full-text citations and supporting documents were then made available to the chapter authors for review. Authors were asked to review all remaining citations and systematically determine whether the citation would be used for background material, discarded (with justification) or used to support a new or existing recommendation. Each citation that was used to formulate, update or revise a recommendation was critically appraised using standardized tools for treatment, diagnostic or prognostic studies with built-in algorithms to ensure consistent approaches to generating levels of evidence, based on prespecified criteria in Table 1. The level of evidence was then determined by the cited paper's objectives, methodological rigour, susceptibility to bias and generalizability (Table 1). Because they could not be critically appraised, meeting abstracts, narrative review articles, news reports and other sources could not be used to support recommendations. Papers evaluating the cost effectiveness of therapies or diagnostic tests also were not included. Finally, citation flow diagrams depicting the search, review and selection of citations for each chapter, specifically, the number of citations reviewed, removed and requiring new or revised recommendations, are included at the end of each chapter (10).

A number of considerations were made when evaluating the evidence within a given area. For example, people with diabetes are at high risk for several sequelae that are not exclusive to diabetes (e.g. cardiovascular disease, renal failure and erectile dysfunction). As such, some evidence relating to these problems was identified that either excluded, did not report on or did not focus on people with diabetes. Whenever such evidence was identified, a level was assigned using the approach described above. Higher levels were assigned if: a) people with diabetes comprised a predefined subgroup; b) the results in the diabetes subgroup were unlikely to have occurred by chance; and c) the evidence was generated in response to questions that were formulated prior to the analysis of the results. Lower levels (than those indicated in Table 1) were assigned to evidence that did not meet these criteria.

Table 1
Criteria for assigning levels of evidence to the published studies

Level	Criteria
Studies of diagnosis	
Level 1	a) Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) b) Independent interpretation of the diagnostic standard (without knowledge of the test result) c) Selection of people suspected (but not known) to have the disorder d) Reproducible description of both the test and diagnostic standard e) At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Non-randomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Level 4	Other
Studies of prognosis	
Level 1	a) Inception cohort of patients with the condition of interest, but free of the outcome of interest b) Reproducible inclusion/exclusion criteria c) Follow up of at least 80% of subjects d) Statistical adjustment for extraneous prognostic factors (confounders) e) Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria

* In cases where such blinding was not possible or was impractical (e.g. intensive vs. conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient.
RCT, randomized controlled trial.

Guideline Development

Expert Committee members evaluated the relevant literature, and guidelines were developed and initially reviewed by the Expert Committee. In the absence of new evidence since the publication of the 2013 Clinical Practice Guidelines, recommendations from the 2013 document were not changed.

The studies used to develop and support each recommendation are cited beside the level of evidence. In some cases, key citations that influenced the final recommendation were not assigned the same level of evidence, but rather were of varying levels of evidence. In those circumstances, all relevant studies were cited, regardless of the grading assigned to the recommendation. The final grading depended on the totality of evidence, including the relative strengths of the studies from a methodological perspective and the studies' findings. Studies with conflicting outcomes were considered and cited in the final recommendation and were assigned a grade to reflect the uncertainty signalled by conflicting findings. Further details on the grading process are described below.

Finally, several treatment recommendations were based on evidence generated from the use of 1 therapeutic agent from a given class (e.g. 1 of the "statins"). Whenever evidence relating to 1 or more agents from a recognized class of agents was available, the recommendation was written so as to be relevant to the class, but specifically studied therapeutic agents were identified within the recommendation and/or cited reference(s). Only medications with Health Canada Notice of Compliance granted by September 15, 2017 were included in the recommendations.

Table 2
Criteria for assigning grades of recommendations for clinical practice

Grade	Criteria
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

Grading the Recommendations

After formulating new recommendations or modifying existing ones based on new evidence, each recommendation was assigned a grade from A through D (Table 2). The highest possible grade that a recommendation could have was based on the strength of evidence that supported the recommendation (i.e. the highest level of evidence assigned to studies on which the recommendation was based). However, the assigned grading was lowered in some cases; for example, if the evidence was found not to be applicable to the Canadian population or, if based on the consensus of the Steering and Executive Committees, there were additional concerns regarding the recommendation. In some situations, the grading also was lowered for subgroups that were not well represented in the study, or in whom the beneficial effect of an intervention was less clear. Grading also was lowered if the findings from relevant (and equally rigorous) studies on the topic were conflicting. Thus, a recommendation based on Level 1 evidence, deemed to be very applicable to Canadians and supported by strong consensus, was assigned a grade of A. A recommendation not deemed to be applicable to Canadians, or judged to require further supporting evidence, was assigned a lower grade. Where available, the number of patients that would need to be treated in order to prevent 1 clinical event (number needed to treat [NNT]) or to cause an adverse event (number needed to harm [NNH]) was considered in assessing the impact of a particular intervention. The degree to which evidence derived from other populations was felt to be relevant to diabetes also was reflected in the wording and grading of the recommendation. Finally, in the absence of Level 1, 2 or 3 supporting evidence, or if the recommendation was based on the consensus of the Steering and Executive Committees, the highest grade that could be assigned was D.

Interpreting the Assigned Grade of a Recommendation

The grade assigned to each recommendation is closely linked to the methodological rigour and robustness of the relevant clinical research. Therefore, as noted above, a high grade reflects a high degree of confidence that following the recommendation will lead to the desired outcome. Similarly, a lower grade reflects weaker evidence, and a greater possibility that the recommendation will change when more evidence is generated in the future. Of note, the assigned grade contains no subjective information regarding the importance of the recommendation or how strongly members of the committee felt about it; it contains information regarding only the evidence upon which the recommendation is based. Thus, many Grade D recommendations were deemed to be very important to the contemporary management of diabetes, based on clinical experience, case series, physiological evidence and current concepts of disease pathophysiology. However, the paucity of clinical evidence addressing the areas of therapy, prevention, diagnosis or prognosis precluded the assignment of a higher grade.

Clearly, clinicians need to base clinical decisions on the best available relevant evidence that addresses clinical situations. However, they also frequently are faced with having to act in the absence of clinical evidence, and there are many situations where good clinical evidence may be impossible, impractical or too expensive to generate (which implies that it would be impossible to develop Grade A recommendations). Varying grades of recommendations, therefore, reflect varying degrees of certainty regarding the strength of inference that can be drawn from the evidence in support of the recommendation. Therefore, these evidence-based guidelines and their graded recommendations are designed to satisfy 2 important needs: 1) the explicit identification of the best research upon which the recommendation is based, and an assessment of its scientific relevance and quality (captured by the assignment of a level of evidence to each citation); and 2) the explicit assignment of strength of the recommendation based on this evidence (captured by the grade). In this way, they provide a convenient summary of the evidence to facilitate clinicians in the task of "weighting" and incorporating ever-increasing evidence into their daily clinical decision-making. They also facilitate the ability of clinicians, health-care planners, health-care providers, and society, in general, to critically examine any recommendation and arrive at their own conclusions regarding its appropriateness. Thus, these guidelines facilitate their own scrutiny by others according to the same principles that they use to scrutinize the literature.

It is important to note that the system chosen for grading recommendations differs from the approach used in some other guideline documents in which a treatment or procedure that is not useful/effective and in some cases may be harmful are assigned a grade or class (11). In this Diabetes Canada guidelines document, recommendation to avoid any harmful practices would be graded in the same manner as all other recommendations. However, it should be noted that the authors of these guidelines focused on clinical practices that were thought to be potentially beneficial, and did not seek out evidence regarding the harmfulness of interventions.

Independent Methodological Review

An Independent Methods Review (IMR) committee was established to ensure consistency and rigour in the recommendation development process. The IMR consisted of 9 university-based clinician faculty with advanced training in research methods (2 co-chairs, and 7 reviewing members). The IMR provided methodological expertise and were a resource available to the recommendation authors throughout the development process.

All drafted recommendations and their supporting evidence were appraised and graded by the recommendation authors. The IMR would then provide a secondary critical review of the recommendation and the evidence to ensure the following: 1) There was strong fidelity between the wording of the recommendation and the cited clinical evidence; and 2) Provide an independent appraisal and grade for the cited evidence. Where appropriate, the IMR would suggest rephrasing of recommendations to ensure the recommendation accurately reflected the underpinning evidence. In the event that there was discordance between the author-assigned grade and the IMR-assigned grade, the recommendation was arbitrated by 1 of the IMR co-chairs. All IMR review activities were systematically performed and recorded to ensure procedural quality and transparency.

External Peer Review

In May 2017, a draft document was circulated nationally and internationally for content review by numerous stakeholders and experts in relevant fields, including specialists, community primary care providers, academic departments of family medicine across Canada, and specialty and disease support organizations. This input was then considered by the Expert, Executive and Steering Committees and revisions were made accordingly. Revised

recommendations were reviewed and approved by the Executive and Steering Committees. Selected recommendations were presented at a professional and public forum at the Diabetes Canada/Canadian Society of Endocrinology and Metabolism Professional Conference and Annual Meetings in Edmonton, Alberta on November 4, 2017.

Disclosure of Conflict of Interest

Expert Committee members were volunteers and received no remuneration or honoraria for their participation. Members of all committees signed an annual duality of interest form listing all financial interests or relationships with manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services. The most recent 2018 disclosures have been included at the end of each chapter. Dualities of interest were discussed during deliberations where relevant. In the case of a potential duality or outright conflict of interest, committee members removed themselves from discussions.

Other Relevant Guidelines

Introduction, p. S1

Author Disclosures

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2018 Clinical Practice Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The chronic hyperglycemia of diabetes is associated with significant long-term microvascular and cardiovascular complications.
- A fasting plasma glucose of ≥7.0 mmol/L, a 2-hour plasma glucose value in a 75 g oral glucose tolerance test of ≥11.1 mmol/L or a glycated hemoglobin (A1C) of ≥6.5% can predict the development of retinopathy. This permits the diagnosis of diabetes to be made on the basis of each of these parameters.
- The term "prediabetes" refers to impaired fasting glucose, impaired glucose tolerance or an A1C of 6.0% to 6.4%, each of which places individuals at increased risk of developing diabetes and its complications.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- There are 2 main types of diabetes. Type 1 diabetes occurs when the pancreas is unable to produce insulin. Type 2 diabetes occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced.
- Gestational diabetes is a type of diabetes that is first recognized or begins during pregnancy.
- Monogenic diabetes is a rare disorder caused by genetic defects of beta cell function.
- Prediabetes refers to blood glucose levels that are higher than normal, but not yet high enough to be diagnosed as type 2 diabetes. Although not everyone with prediabetes will develop type 2 diabetes, many people will.
- You should discuss the type of diabetes you have with your diabetes health-care team.
- There are several types of blood tests that can be done to determine if a person has diabetes and, in most cases, a confirmatory blood test is required to be sure.

Definition of Diabetes and Prediabetes

Diabetes mellitus is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy.

"Prediabetes" is a practical and convenient term referring to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) (1) or a glycated hemoglobin (A1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications.

Classification of Diabetes

The majority of cases of diabetes can be broadly classified into 2 categories: type 1 diabetes and type 2 diabetes, although some cases are difficult to classify. Gestational diabetes (GDM) refers to glucose intolerance with onset or first recognition during pregnancy. The classification of diabetes is summarized in Table 1. Appendix 2 addresses the etiologic classification of diabetes, including less common forms associated with genetic mutations, diseases of the exocrine pancreas (such as cystic fibrosis), other diseases or drug exposure (such as glucocorticoids, medications to treat HIV/AIDS, and atypical antipsychotics).

Monogenic diabetes is a rare disorder caused by genetic defects of beta cell function that typically presents in young people (<25 years of age), is noninsulin dependent and is familial, with an autosomal dominant pattern of inheritance (2). Differentiating between type 1, type 2 and monogenic diabetes is important but can be difficult at the time of diagnosis in certain situations. Table 2 highlights the main features of type 1 diabetes, including LADA form, type 2 diabetes and monogenic diabetes. No diagnostic test or clinical

Table 1
Classification of diabetes

- **Type 1 diabetes*** encompasses diabetes that is primarily a result of pancreatic beta cell destruction with consequent insulin deficiency, which is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.
- **Type 2 diabetes** may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance. Ketosis is not as common.
- **Gestational diabetes mellitus** refers to glucose intolerance with onset or first recognition during pregnancy.
- **Other specific types** include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (see Appendix 2. Etiologic Classification of Diabetes Mellitus).

* Includes **latent autoimmune diabetes in adults (LADA)**; the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (5).

Conflict of interest statements can be found on page S14.

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Table 2
Clinical features distinguishing type 1 diabetes, type 2 diabetes and monogenic diabetes

Clinical features	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes
Age of onset (years)	Most <25 but can occur at any age (but not before the age of 6 months)	Usually >25 but incidence increasing in adolescents, paralleling increasing rate of obesity in children and adolescents	Usually <25; neonatal diabetes <6 months*
Weight	Usually thin, but, with obesity epidemic, can have overweight or obesity	>90% at least overweight	Similar to general population
Islet autoantibodies	Usually present	Absent	Absent
C-peptide	Undetectable/low	Normal/high	Normal
Insulin production	Absent	Present	Usually present
First-line treatment	Insulin	Noninsulin antihyperglycemic agents, gradual dependence on insulin may occur	Depends on subtype
Family history of diabetes	Infrequent (5%–10%)	Frequent (75%–90%)	Multigenerational, autosomal pattern of inheritance
DKA	Common	Rare	Rare (except for neonatal diabetes*)

DKA, diabetic ketoacidosis.
* Neonatal diabetes is a form of diabetes with onset <6 months of age, requires genetic testing, and may be amenable to therapy with oral sulfonylurea in place of insulin therapy (3).

criteria can reliably make this distinction, but additional testing may be helpful in atypical presentations if knowing the specific diagnosis may alter management. One monogenic form to highlight is neonatal diabetes, which typically presents by 6 months of age and is indistinguishable from type 1 diabetes in its clinical features, but may be amenable to therapy with oral sulfonylurea in place of insulin therapy. For this reason, all infants diagnosed before 6 months of age should have genetic testing. In addition, all people with a diagnosis of type 1 diabetes should be reviewed to determine if diagnosis occurred prior to 6 months of age and, if so, genetic testing should be performed (3).

Obesity and physical signs of insulin resistance (e.g. acanthosis nigricans) are more common in children and adolescents with type 2 diabetes than type 1 diabetes. In adults, a systematic review of clinical indicators identified age at diagnosis of diabetes <30 to 40 years, and time to needing insulin <1 to 2 years as more predictive of type 1 diabetes than body mass index (BMI) (4).

The presence of autoimmune markers, such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell (ICA) autoantibodies, may be helpful in identifying type 1 diabetes and rapid progression to insulin requirement (5), but levels wane over time and they do not have sufficient diagnostic accuracy to be used routinely (6). In cases where it is difficult to distinguish between type 1, type 2 and monogenic diabetes, presence of 1 or more autoantibodies (GAD and ICA) indicates type 1 diabetes with a need for insulin replacement therapy; however, the absence of autoantibodies does not rule out type 1 diabetes. If the person has clinical features suggestive of monogenic diabetes (familial diabetes with autosomal dominant pattern of inheritance >2 generations, onset <25 years, not having obesity), genetic testing for monogenic diabetes may be performed (7).

While very low C-peptide levels measured after months of clinical stabilization may favour type 1 diabetes (8), they are not helpful in acute hyperglycemia (9,10). Combined use of autoantibody testing and C-peptide measurement at diagnosis may have diagnostic and prognostic utility in pediatric diabetes, but requires further study (11) (see Type 2 Diabetes in Children and Adolescents chapter, p. S247). One study found that, among individuals presenting in diabetic ketoacidosis (DKA), those with 3 negative antibodies and fasting C-peptide levels >0.33 nmol/L (1 to 3 weeks after resolution of the DKA and 10 hours after the last dose of rapid- or intermediate-acting insulin or metformin, and 24 hours after the last dose of sulfonylurea or long-acting insulin) were often able to discontinue insulin, and be treated with noninsulin antihyperglycemic agents when blood glucose (BG) rose (12). Genetic risk scoring for type 1 diabetes may provide marginal additional information over clinical features and autoantibodies, but it is too early to know its utility in clinical practice (13). Clinical judgement with safe management and ongoing follow up is a prudent approach for all people diagnosed with diabetes, regardless of the type.

Diagnostic Criteria

Diabetes

The diagnostic criteria for diabetes are summarized in Table 3 (1). These criteria are based on venous samples and laboratory methods (14). A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose (2hPG) value of ≥11.1 mmol/L in a 75 g oral glucose tolerance test (OGTT), and

Table 3
Diagnosis of diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
A1C ≥6.5% (in adults)
Using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C and not for suspected type 1 diabetes (see text)
or
2hPG in a 75 g OGTT ≥11.1 mmol/L
or
Random PG ≥11.1 mmol/L
Random = any time of the day, without regard to the interval since the last meal

In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. If results of 2 different tests are available and both are above the diagnostic thresholds, the diagnosis of diabetes is confirmed.
To avoid rapid metabolic deterioration in individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), the initiation of treatment should not be delayed in order to complete confirmatory testing.

2hPG, 2-hour plasma glucose; *AlC*, glycated hemoglobin; *FPG*, fasting plasma glucose; OGTT, oral glucose tolerance test; *PG*, plasma glucose.

Table 4
Advantages and disadvantages of diagnostic tests for diabetes* (43)

Parameter	Advantages	Disadvantages
FPG	• Established standard • Fast and easy • Single sample • Predicts microvascular complications	• Sample not stable • High day-to-day variability • Inconvenient (fasting) • Reflects glucose homeostasis at a single point in time
2hPG in a 75 g OGTT	• Established standard • Predicts microvascular complications	• Sample not stable • High day-to-day variability • Inconvenient • Unpalatable • Cost
A1C	• Convenient (measure any time of day) • Single sample • Predicts microvascular complications • Better predictor of CVD than FPG or 2hPG in a 75 g OGTT • Low day-to-day variability • Reflects long-term glucose concentration	• Cost • Misleading in various medical conditions (e.g. hemoglobinopathies, iron deficiency, hemolytic anemia, severe hepatic or renal disease) • Altered by ethnicity and aging • Standardized, validated assay required • Not for diagnostic use in children and adolescents† (as the sole diagnostic test), pregnant women as part of routine screening for gestational diabetes‡, those with cystic fibrosis or those with suspected type 1 diabetes

2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *CVD*, cardiovascular disease; *FPG*, fasting plasma glucose; *OGTT*, oral glucose tolerance test.
* Adapted from Sacks D. A1C versus glucose testing: a comparison (43).
† See Type 2 Diabetes in Children and Adolescents chapter, p. S247.
‡ See Diabetes and Pregnancy chapter, p. S255.

each predicts the development of retinopathy (15). The relationship between A1C and retinopathy is similar to that of FPG or 2hPG with a threshold at around 6.5% (2,16–22). Although the diagnosis of diabetes is based on an A1C threshold for developing microvascular disease, A1C is also a continuous cardiovascular (CV) risk factor and a better predictor of CV events than FPG or 2hPG (23,24). Although very specific, A1C is less sensitive to diagnose diabetes than traditional glucose criteria, there are, however, several advantages to using A1C for diabetes diagnosis (25,26). A1C can be measured at any time of day and is more convenient than FPG or 2hPG in a 75 g OGTT. A1C testing also avoids the problem of day-to-day variability of glucose values as it reflects the average plasma glucose (PG) over the previous 2 to 3 months (1). In a Canadian context, A1C may identify more people as having diabetes than FPG (27). However, other studies suggest A1C may not identify as many people as having diabetes compared to FPG or 2hPG (28).

In order to use A1C as a diagnostic criterion, A1C must be measured using a validated assay standardized to the National Glycohemoglobin Standardization Program—Diabetes Control and Complications Trial reference. It is important to note that A1C may be misleading in individuals with various hemoglobinopathies, hemolytic or iron deficiency anemias, iron deficiency without anemia, Graves' disease and severe hepatic and renal disease (29–32), although some evidence suggests that A1C may not be affected by these conditions in people without diabetes (33) (see Monitoring Glycemic Control chapter, p. S47). Studies also show the relationship between glucose levels and A1C varies between people living at extremes of altitude (34). In addition, studies of various ethnicities indicate that African Americans, American Indians, Hispanics and Asians have A1C values that are up to 0.4% higher than those of non-Hispanic white individuals at similar levels of glycemia (35–38), suggesting people from these ethnic groups would have a higher chance of being diagnosed with diabetes by current A1C criteria. Research is required to determine if A1C levels differ in Canadians of African descent or Indigenous peoples. The frequency of retinopathy begins to increase at lower A1C levels in African-Americans than in Caucasians, which suggests a lower threshold for diagnosing diabetes in persons of African descent may be needed (39), whereas a threshold of 6.5% for predicting retinopathy has been validated in large Japanese and Asian cohorts (20,21). A1C values also are affected by age, rising by up to 0.1% per decade of life (40,41). More studies may help to determine if age- or ethnic-specific adjusted A1C thresholds are required for diabetes diagnosis. In addition, A1C is not recommended for diagnostic purposes in children and adolescents (as the sole diagnostic test), pregnant women as part of routine screening for gestational diabetes, those with cystic fibrosis (42) or those with suspected type 1 diabetes (see Diabetes and Pregnancy chapter, p. S255; Type 2 Diabetes in Children and Adolescents chapter, p. S247).

Other measures of glycemia, such as fructosamine, glycated albumin and 1,5-anhydroglucitol have not been validated for the diagnosis of diabetes.

The decision of which test to use for diabetes diagnosis is left to clinical judgement (Table 3). Each diagnostic test has advantages and disadvantages (43) (Table 4). In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. Such an approach confirms the diagnosis of diabetes in approximately 40% to 90% of people with an initial positive test (26,44). It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated.

In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of 2 different tests are available and both are above the diagnostic cut points, the diagnosis of diabetes is confirmed. When the results of more than 1 test are available (among FPG, A1C, 2hPG in a 75 g OGTT) and the results are discordant, the test whose result is above the diagnostic cut point should be repeated and the diagnosis made on the basis of the repeat test.

Prediabetes

The term "prediabetes" refers to IFG, IGT or an A1C of 6.0% to 6.4% (Table 5), each of which places individuals at high risk of developing diabetes and its complications. Not all individuals with prediabetes will necessarily progress along the continuum of

Table 5
Diagnosis of prediabetes

Test	Result	Prediabetes category
FPG (mmol/L)	6.1–6.9	IFG
2hPG in a 75 g OGTT (mmol/L)	7.8–11.0	IGT
A1C (%)	6.0–6.4	Prediabetes

2hPG, 2-hour plasma glucose; *AlC,* glycated hemoglobin; *FPG,* fasting plasma glucose; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; OGTT, oral glucose tolerance test.

Table 6
Harmonized definition of the metabolic syndrome: ≥3 measures to make the diagnosis of metabolic syndrome* (35)

Measure	Categorical thresholds	
	Men	Women
Elevated waist circumference (cm)(population and country specific cut points):		
• Canada; USA.	≥102	≥88
• Europids; Middle-Eastern; Sub-Saharan African; Mediterranean	≥94	≥80
• Asians; Japanese; South and Central Americans	≥90	≥80
Elevated TG (mmol/L) (drug treatment for elevated TG is an alternate indicator†)	≥1.7	
Reduced HDL-C (mmol/L) (drug treatment for reduced HDL-C is an alternate indicator†)	<1.0	<1.3
Elevated BP (mmHg) (antihypertensive drug treatment in a person with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85	
Elevated FPG (mmol/L) (drug treatment of elevated glucose is an alternate indicator)	≥5.6	

BP, blood pressure; *FPG*, fasting plasma glucose; *HDL-C,* high-density lipoprotein cholesterol; *TG*, triglycerides.

* Adapted from: Alberti KG, Eckel R, Grundy S, et al. Harmonizing the metabolic syndrome (53).

† The most commonly used drugs for elevated TG and reduced HDL-C are fibrates and nicotinic acid. A person taking one of these drugs can be presumed to have high TG and reduced HDL-C. High-dose omega-3 fatty acids presumes high TG.

dysglycemia to develop diabetes. Indeed, a significant proportion of people who are diagnosed with IFG or IGT will revert to normoglycemia. While people with prediabetes do not have increased risk for microvascular disease as seen in diabetes, they are at risk for the development of diabetes and CVD (45–47). Due to variability in the literature, it seems that IGT may or may not be more strongly associated with CVD outcomes than IFG, and A1C may or may not be more strongly associated with CVD outcomes than either IFG or IGT. Individuals identified as having both IFG and IGT are at higher risk for diabetes as well as CVD than people with either IFG or IGT alone. People with prediabetes, particularly in the context of the metabolic syndrome, would benefit from CV risk factor modification.

While there is no worldwide consensus on the definition of IFG (48,49), Diabetes Canada defines IFG as an FPG value of 6.1 to 6.9 mmol/L due to the higher risk of developing diabetes in these individuals compared to defining IFG as an FPG value of 5.6 to 6.9 mmol/L (49). While there is a continuum of risk for diabetes in individuals with A1C levels between 5.5% to 6.4%, population studies demonstrate that A1C levels of 6.0% to 6.4% are associated with a higher risk for diabetes compared to levels between 5.5% to 6.0% (50). While the American Diabetes Association defines prediabetes as an A1C between 5.7% to 6.4%, Diabetes Canada has based the definition on a higher risk group and includes an A1C of 6.0% to 6.4% as a diagnostic criterion for prediabetes (1). However, A1C levels <6.0% can indeed be associated with an increased risk for diabetes (50). The combination of an FPG of 6.1 to 6.9 mmol/L and an A1C of 6.0% to 6.4% is predictive of 100% progression to type 2 diabetes over a 5-year period (51).

Metabolic Syndrome

Prediabetes and type 2 diabetes are often manifestations of a much broader underlying disorder (52), including the metabolic syndrome, a highly prevalent, multifaceted condition characterized by a constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia and elevated BG. Individuals with the metabolic syndrome are at significant risk of developing CVD. While metabolic syndrome and type 2 diabetes often coexist, those with metabolic syndrome without diabetes are at significant risk of developing diabetes. Evidence exists to support an aggressive approach to identifying and treating people, not only those with hyperglycemia, but also those with the associated CV risk factors that make up the metabolic syndrome, such as hypertension, dyslipidemia and abdominal obesity, in the hope of significantly reducing CV morbidity and mortality.

Various diagnostic criteria for the metabolic syndrome have been proposed. In 2009, a harmonized definition of the metabolic syndrome was established, with at least 3 or more criteria required for diagnosis (53) (Table 6).

RECOMMENDATIONS

1. Diabetes should be diagnosed by any of the following criteria:
   a. FPG ≥7.0 mmol/L [Grade B, Level 2 (54)]
   b. A1C ≥6.5% (for use in adults in the absence of factors that affect the accuracy of A1C and not for use in those with suspected type 1 diabetes) [Grade B, Level 2 (20,21,54)]
   c. 2hPG in a 75 g OGTT ≥11.1 mmol/L [Grade B, Level 2 (54)]
   d. Random PG ≥11.1 mmol/L [Grade D, Consensus].

   In the presence of symptoms of hyperglycemia, a single test result in the diabetes range is sufficient to make the diagnosis of diabetes. In the absence of symptoms of hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. If results of 2 different tests are available and both are above the diagnostic cut points the diagnosis of diabetes is confirmed [Grade D, Consensus].

   To avoid rapid metabolic deterioration in individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), the initiation of treatment should not be delayed in order to complete confirmatory testing [Grade D, Consensus].

2. Prediabetes (defined as a state which places individuals at high risk of developing diabetes and its complications) is diagnosed by any of the following criteria:
   a. IFG (FPG 6.1–6.9 mmol/L) [Grade A, Level 1 (45)]
   b. IGT (2hPG in a 75 g OGTT 7.8–11.0 mmol/L) [Grade A, Level 1 (45)]
   c. A1C 6.0%–6.4% (for use in adults in the absence of factors that affect the accuracy of A1C and not for use in suspected type 1 diabetes) [Grade B, Level 2 (50)].

Abbreviations:
2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *BG*; blood glucose; *FPG*, fasting plasma glucose; *DKA*, diabetic ketoacidosis; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OGTT*, oral glucose tolerance test; *PG*, plasma glucose.

Other Relevant Guidelines

Screening for Diabetes in Adults, p. S16
Reducing the Risk of Developing Diabetes, p. S20
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247

Relevant Appendix

Appendix 2. Etiologic Classification of Diabetes

Author Disclosures

Dr. Punthakee reports research contracts from Amgen, AstraZeneca/Bristol Myers Squibb, Lexicon, Merck, Novo Nordisk, and Sanofi, personal fees from Abbott, AstraZeneca/Bristol Myers Squibb, Boehringer Ingelheim/Eli Lilly, Janssen, Merck, Novo Nordisk, Pfizer, and Sanofi, outside the submitted work. Dr. Goldenberg reports personal fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier, outside the submitted work. Dr. Katz has nothing to disclose.

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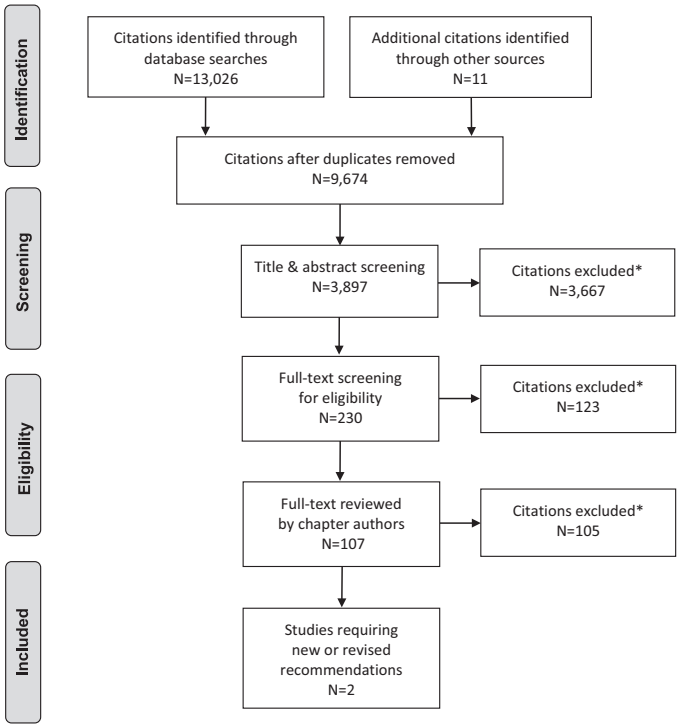
Literature Review Flow Diagram for Chapter 3: Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (55).

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2018 Clinical Practice Guidelines

Screening for Diabetes in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

Jean-Marie Ekoe MD, CSPQ, PD, Ronald Goldenberg MD, FRCPC, FACE, Pamela Katz MD, FRCPC

KEY MESSAGES

- In the absence of evidence for interventions to prevent or delay type 1 diabetes, routine screening for type 1 diabetes is not recommended.
- Screen for type 2 diabetes using a fasting plasma glucose and/or glycated hemoglobin (A1C) every 3 years in individuals ≥40 years of age or in individuals at high risk on a risk calculator (33% chance of developing diabetes over 10 years).
- Diagnose diabetes in the absence of symptomatic hyperglycemia if A1C is ≥6.5% on 2 tests, fasting plasma glucose ≥7.0 mmol/L on 2 tests, or A1C ≥6.5% and fasting plasma glucose ≥7.0 mmol/L (see Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).

KEY MESSAGES FOR PEOPLE WITH DIABETES

- If you are age 40 years or over, you are at risk for type 2 diabetes and should be tested at least every 3 years.
- If you have risk factors that increase the likelihood of developing type 2 diabetes, you should be tested more frequently and/or start regular screening earlier. Some of the risk factors include family history of diabetes; being a member of a high-risk population; history of prediabetes or gestational diabetes; and having overweight.
- You can use the Canadian Diabetes Risk (CANRISK) calculator to assess your risk for diabetes (available at http://www.healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/diabetes-diabete/canrisk/index-eng.php).
- Several methods for screening for diabetes are available. Usually 2 abnormal blood tests are needed to make a diagnosis of diabetes.
- The earlier you are diagnosed, the sooner you can take action to stay well.

Introduction

Screening for diabetes implies testing for diabetes in individuals without symptoms who are unaware of their condition. Screening for diabetes will also detect individuals at increased risk for diabetes (prediabetes) or individuals with less severe states of dysglycemia who may still be at risk for type 2 diabetes. Screening strategies vary according to the type of diabetes and evidence of effective interventions to prevent progression of prediabetes to diabetes and/or reduce the risk of complications associated with diabetes. A large meta-analysis suggests that interventions in people classified through screening as having prediabetes have some efficacy in preventing or delaying onset of type 2 diabetes in trial populations (1) (see Reducing the Risk of Developing Diabetes chapter, p. S20). The growing importance of diabetes screening is undeniable (2).

In contrast to other diseases, there is no distinction between screening and diagnostic testing. Therefore, to screen for diabetes and prediabetes, the same tests would be used for diagnosis of both medical conditions (see Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).

Screening for Type 1 Diabetes

Type 1 diabetes mellitus is primarily a result of pancreatic beta-cell destruction due to an immune-mediated process that is likely incited by environmental factors in genetically predisposed individuals. An individual's risk of developing type 1 diabetes can be estimated by considering family history of type 1 diabetes with attention to age of onset and sex of the affected family members (3) and profiling immunity and genetic markers (4).

The loss of pancreatic beta cells in the development of type 1 diabetes passes through a subclinical prodrome that can be detected reliably in first- and second-degree relatives of persons with type 1 diabetes by the presence of pancreatic islet autoantibodies in their sera (5). However, in a recent large study, one-time screening for glutamic acid decarboxylase antibodies (GADAs) and islet antigen-2 antibodies (IA-2As) in the general childhood population in Finland would identify only 60% of those individuals who will develop type 1 diabetes over the next 27 years. Initial positivity for GADAs and/or IA-2As had a sensitivity of 61% (95% confidence interval [CI] 36–83) for type 1 diabetes. The combined positivity for GADAs and IA-2As had both a specificity and a positive predictive value of 100% (95% CI 59–100) (6).

Ongoing clinical studies are testing different strategies for preventing or reversing early type 1 diabetes in the presence of positive autoimmunity. Given that the various serological markers are not universally available and in the absence of evidence for interventions to prevent or delay type 1 diabetes, no widespread recommendations for screening for type 1 diabetes can be made.

Screening for Type 2 Diabetes in Adults

A substantial number of Canadians are living with diabetes that has not yet been diagnosed. The estimated prevalence of

Conflict of interest statements can be found on page S18.

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undiagnosed type 2 diabetes in the general population is 1.13% by fasting plasma glucose (FPG) levels and 3.09% by glycated hemoglobin (A1C) criterion, contributing to 20% to 40% of total diabetes cases (7). Based on retinopathy data, it is estimated that the onset of type 2 diabetes occurs 4 to 7 years before its clinical diagnosis (8,9). Tests for hyperglycemia can identify individuals who may have or be at risk for preventable diabetes complications (6,10).

To be effective, population-based screening would have to involve wide coverage and would have the goal of early identification and subsequent intervention to reduce morbidity and mortality. Using various multi-staged screening strategies, the ADDITION-Europe study showed that 20% to 94% of eligible people in primary care practices attended the first blood glucose test of the screening process, and diabetes was detected in 0.33% to 1.09% of the target populations, which was lower than expected (11). In the subsequent ADDITION Europe cluster randomized trial of intensive multifaceted cardiovascular (CV) risk factor management vs. routine diabetes care among screening-identified people with type 2 diabetes, intensive management did not significantly reduce CV [hazard ratio (HR) 0.83, 95% CI 0.65–1.05] or all-cause mortality (HR 0.91, 95% CI 0.69–1.21) (12). Of note, a very high proportion of the routine care group also received optimal CV risk factor management, which may have diluted any potential benefits. When a computer simulation model was used to estimate the effect associated with screening and intensive treatment compared to a 3- to 6-year delay in diagnosis, a significant reduction in the risk of CV outcomes was seen with early detection and treatment, although this type of study has several inherent limitations (13).

In ADDITION-Cambridge, population-based screening for type 2 diabetes was not associated with a reduction in all-cause, CV or diabetes-related mortality within 10 years compared to a no-screening control group. However, the low rate of type 2 diabetes in the screened population (3%) was likely too small to affect overall population mortality (14). Nonetheless, there is currently insufficient evidence of clinical benefit to support a strategy of population-based screening for type 2 diabetes.

In 2015, the States Preventive Services Task Force (USPSTF) recommended targeted screening for abnormal blood glucose (BG) in adults aged 40 to 70 years with overweight or obesity (15). However, screening according to this recommendation would only detect approximately half of people with undiagnosed dysglycemia, and substantially less in racial/ethnic minorities (16). Although the relatively low prevalence of diabetes in the general population makes it unlikely that mass screening will be cost effective, testing for diabetes in people with risk factors for type 2 diabetes (Table 1), or with diabetes-associated conditions, is likely to result in more benefit than harm and will lead to overall cost savings (17–23). Therefore, in contrast to the USPSTF, Diabetes Canada guidelines recommend broader inclusion criteria for screening based on the presence of additional risk factors. Routine testing for type 2 diabetes is justifiable in some, but not all, settings (24,25). Screening individuals as early as age 40 years in primary care offices has proven to be useful in detecting unrecognized diabetes (26).

While fasting plasma glucose (FPG) and/or A1C are the recommended screening tests, a 75 g oral glucose tolerance test (OGTT) may be considered when the FPG is 6.1 to 6.9 mmol/L (19) and/or A1C is 6.0% to 6.4% (Figure 1). In one study, A1C identified only one-half of people with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) diagnosed by OGTT (27). OGTT may also be considered when the FPG is 5.6 to 6.0 mmol/L and/or A1C is 5.5% to 5.9% and suspicion of type 2 diabetes or IGT is high (e.g. for individuals with risk factors listed in Table 1). Along with the glycemic criteria for considering an OGTT, testing may be especially useful in the following clinical situations: unexplained microvascular complications, diagnostic uncertainty (e.g. presence of factors that make A1C inaccurate) or if further CV risk stratification is considered to be beneficial.

Table 1
Risk factors for type 2 diabetes

- Age ≥40 years
- First-degree relative with type 2 diabetes
- Member of high-risk population (e.g. African, Arab, Asian, Hispanic, Indigenous or South Asian descent, low socioeconomic status)
- History of prediabetes (IGT, IFG or A1C 6.0%–6.4%)*
- History of GDM
- History of delivery of a macrosomic infant
- Presence of end organ damage associated with diabetes:
  - Microvascular (retinopathy, neuropathy, nephropathy)
  - CV (coronary, cerebrovascular, peripheral)
- Presence of vascular risk factors:
  - HDL-C <1.0 mmol/L in males, <1.3 mmol/L in females*
  - TG ≥1.7 mmol/L*
  - Hypertension*
  - Overweight*
  - Abdominal obesity*
  - Smoking
- Presence of associated diseases:
  - History of pancreatitis
  - Polycystic ovary syndrome*
  - Acanthosis nigricans*
  - Hyperuricemia/gout
  - Non-alcoholic steatohepatitis
  - Psychiatric disorders (bipolar disorder, depression, schizophrenia†)
  - HIV infection‡
  - Obstructive sleep apnea§
  - Cystic fibrosis
- Use of drugs associated with diabetes:
  - Glucocorticoids
  - Atypical antipsychotics
  - Statins
  - Highly active antiretroviral therapy‡
  - Anti-rejection drugs
  - Other (see Appendix 2)
- Other secondary causes (see Appendix 2)

A1C, glycated hemoglobin; *CV*, cardiovascular; *GDM*, gestational diabetes; *HDL-C*, high-density lipoprotein cholesterol; *HIV*, human immunodeficiency virus-1; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance.

* Associated with insulin resistance.

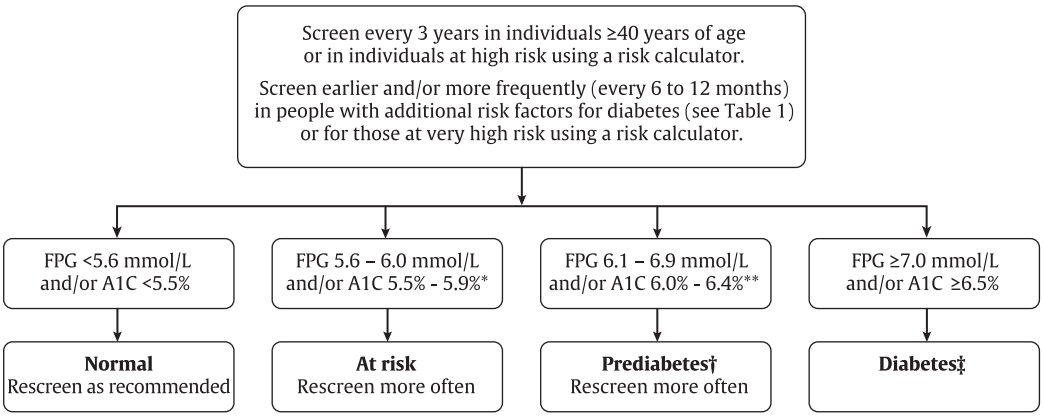
† The incidence of type 2 diabetes is at least 3 times higher in people with schizophrenia than in the general population (34,35). Using data collected in 1991, the prevalence of diabetes was assessed in >20,000 individuals diagnosed with schizophrenia. The rate of diagnosed diabetes was 9% to 14%, exceeding rates for the general population prior to the widespread use of new antipsychotic drugs (36).

‡ HIV and HAART increase the risk of prediabetes (IGT) and type 2 diabetes by 1.5- to 4-fold compared to the general population (37).

§ Obstructive sleep apnea is an independent risk factor for diabetes (hazard ratio 1.43) (38).

People with prediabetes, especially those with IGT or an A1C of 6.0% to 6.4%, not only are at increased risk of developing type 2 diabetes, but also have an increased risk of CV complications, particularly in the context of the metabolic syndrome (28,29). The increased risk of cardiovascular disease (CVD) in people with IGT is a factor supporting ongoing consideration of the 75 g OGTT in diabetes screening. These individuals would benefit from CV risk factor reduction strategies (2).

Members of high-risk ethnic populations should be screened for prediabetes and type 2 diabetes using the recommended screening tests, such as FPG, A1C and OGTT (Table 1). However, the high prevalence of hemoglobinopathies among these populations may considerably reduce the accuracy of A1C as a reliable screening tool. Furthermore, high-risk ethnic groups may have A1C levels that are slightly higher than those of Caucasians at the same level of glycemia, and more studies may help determine ethnic-specific A1C thresholds for diabetes diagnosis (30) (see Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).



If both FPG and A1C are available, but discordant, use the test that appears furthest to the right side of the algorithm.

*Consider 75 g OGTT if ≥1 risk factors; ** Consider 75 g OGTT (see Tables 3 and 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10 for interpretation of 75 g OGTT).

†Prediabetes = IFG or A1C 6.0 to 6.4% (see Table 5 in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10).

‡In the presence of symptoms of hyperglycemia, a single test result in the diabetes range is sufficient to make the diagnosis of diabetes. In the absence of symptoms of hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. If results of two different tests are available and both are above the diagnostic cut points the diagnosis of diabetes is confirmed.

A1C, glycated hemoglobin; *FPG,* fasting plasma glucose; *IFG,* impaired fasting glucose

Figure 1. Screening and diagnosis algorithm for type 2 diabetes.

Risk Prediction Tools for Type 2 Diabetes

A number of risk scores based on clinical characteristics have been developed to identify individuals at high risk of having undiagnosed diabetes. However, the impact of known risk factors on having undiagnosed type 2 diabetes differs between populations of different ethnic origins, and risk scores developed in Caucasian populations cannot be applied to populations of other ethnic groups (31). Furthermore, the prevalence of individuals at risk for developing type 2 diabetes varies considerably according to the scoring system and diagnostic criteria used. As a result, risk scoring systems must be validated for each considered population in order to adequately detect individuals at risk and eventually implement effective prevention strategies (32). The Canadian Diabetes Risk Assessment Questionnaire (CANRISK) is a statistically valid tool that may be suitable for diabetes risk assessment in Canada's multi-ethnic population and is available on the Internet at www.phac-aspc.gc.ca/cd-mc/diabetes-diabete/canrisk/index-eng.php (33). CANRISK has not been validated in individuals <40 years of age, and should be used with caution in this age group.

RECOMMENDATIONS

1. All individuals should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria [Grade D, Consensus].

2. Screening for diabetes using FPG and/or A1C should be performed every 3 years in individuals ≥40 years of age or at high risk using a risk calculator [Grade D, Consensus]. Earlier testing and/or more frequent follow up (every 6 to 12 months) with either FPG and/or A1C should be considered in those at very high risk using a risk calculator or in people with additional risk factors for diabetes [Grade D, Consensus] (see Table 1 for risk factors).

Abbreviations:
2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *CI*, confidence interval; *CV*, cardiovascular; *FPG*, fasting plasma glucose; *GADAs*; glutamic acid decarboxylase antibodies; *GDM*, gestational diabetes; *HAART*, highly active antiretroviral therapy; *HDL-C*, high-density lipoprotein cholesterol; *HIV*; human immunodeficiency virus-1; *HR*, hazard ratio; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OGTT*, oral glucose tolerance test.

Other Relevant Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S10
Reducing the Risk of Developing Diabetes, p. S20
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247

Relevant Appendix

Appendix 2. Etiologic Classification of Diabetes Mellitus

Author Disclosures

Dr. Goldenberg reports personal fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Sanofi, and Servier, outside the submitted work. No other authors have anything to disclose.

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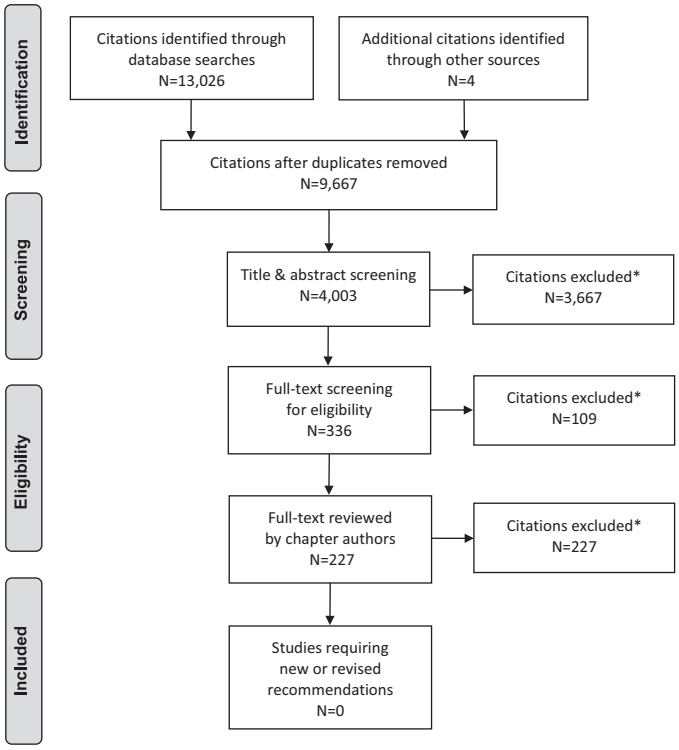
Literature Review Flow Diagram for Chapter 4: Screening for Diabetes in Adults



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (39).

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2018 Clinical Practice Guidelines

Reducing the Risk of Developing Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.
- Intensive and structured healthy behaviour interventions, ideally resulting in loss of approximately 5% of initial body weight, can reduce the risk of progression from impaired fasting glucose or impaired glucose tolerance to type 2 diabetes by almost 60%. When initiated early, the effects of healthy behaviour interventions are long lasting (more than 20 years).
- Progression from prediabetes to type 2 diabetes can also be reduced by pharmacologic therapy with metformin (~30% reduction), with persistent benefits observed after more than 10 years of stopping treatment in the Diabetes Prevention Program.

KEY MESSAGES FOR PEOPLE WITH PREDIABETES

- If you have prediabetes, healthy behaviour changes that result in a loss of 5% of your initial body weight can delay or prevent type 2 diabetes from developing.
- A registered dietitian can educate you about dietary changes that may help reduce your risk for developing diabetes.
- Regular physical activity is also important to reduce your risk of diabetes.
- If healthy behaviour changes are not enough to normalize your blood glucose, your health-care provider may recommend that you use medication in addition to ongoing healthy behaviour changes to manage your prediabetes.

Introduction

Ideal prevention strategies for both type 1 and type 2 diabetes should range from efforts focused on individuals identified as being at risk for developing diabetes to broader group- and population-based strategies. Prevention or delay in the onset of diabetes should not only alleviate the burden of the disease on the individual, but could also decrease the associated morbidity and mortality. Ideal prevention strategies would differ depending on the type of diabetes. Given its increasing incidence and prevalence, the development of safe and cost-effective interventions to reduce the risk of developing diabetes are urgently needed to decrease the burden on individuals and the health-care system.

Reducing the Risk of Developing Type 1 Diabetes

Type 1 diabetes is a chronic autoimmune condition characterized by destruction of pancreatic beta cells. The causes are multifactorial, with both genetic and environmental factors. The exact nature of causative environmental factors continues to be debated. There is a long preclinical period before the onset of overt symptoms, which may be amenable to therapeutic intervention to prevent disease. Immunotherapeutic interventions continue to be the main focus of type 1 diabetes prevention.

Two major trials of interventions to prevent or delay the onset of type 1 diabetes have been completed. The European Nicotinamide Diabetes Intervention Trial (ENDIT), a randomized, double-blind, placebo-controlled trial of high-dose nicotinamide therapy, recruited first-degree relatives of people who were <20 years of age when diagnosed with type 1 diabetes, islet cell antibody positive, <40 years of age and who had a normal oral glucose tolerance test (OGTT). Although nicotinamide was protective in animal studies, no effect was observed in ENDIT during the 5-year trial period (1). The Diabetes Prevention Trial-Type 1 (DPT-1) studied the efficacy of low-dose insulin injections in high-risk (projected 5-year risk of >50%) first-degree relatives of people with type 1 diabetes. Overall, the insulin treatments had no effect (2), but in a subset of participants with high levels of insulin autoantibodies, a delay, and perhaps a reduction, in the incidence of type 1 diabetes was observed (3). A third ongoing large trial, the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study, is investigating the effect of excluding cow's milk protein and replacing it with hydrolyzed formula milk in genetically at-risk infants until 6 to 8 months of age. Preliminary data showed no reduction in the development of diabetes antibodies at age 6 (4), but data on the overt development of diabetes by age 10 is not yet available (5).

A second strategy is to try to halt, at the time of diagnosis, the immune-mediated destruction of beta cells to preserve any residual capacity to produce insulin. Progress in the field has been slow due to safety considerations; namely, side effects from immunosuppression/modulation must be minimized before consideration can be given for clinical use, especially because of the reasonable life expectancy of people with type 1 diabetes and technological advancements with insulin replacement therapy.

As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.

Conflict of interest statements can be found on page S25.

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Reducing the Risk of Developing Type 2 Diabetes

Preventing type 2 diabetes may result in significant public health benefits, including lower rates of cardiovascular disease (CVD), renal failure, blindness and premature mortality (6). An epidemiological analysis projected that if all diabetes could be avoided in Caucasian American males through effective primary prevention, the risk of all-cause and cardiovascular (CV) mortality in the entire population could be reduced by up to 6.2% and 9.0%, respectively (7). Data from the United States indicates that 28% of CV expenditures are attributable to diabetes (8).

Primary approaches to preventing diabetes in a population include the following: 1) programs targeting high-risk individuals [such as those with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or obesity]; 2) programs targeting high-risk subgroups, such as high-risk ethnic groups; and 3) programs for the general population, such as those designed to promote physical activity and healthy eating in adults or children (9–11).

Prospective cohort studies have identified historical, physical and biochemical variables associated with the development of type 2 diabetes. These include older age, family history of type 2 diabetes, certain ethnic backgrounds, prediabetes, history of gestational diabetes, CVD and obesity (especially abdominal obesity), (12–14) and are detailed in Table 1 of the Screening for Diabetes in Adults chapter, p. S16. Results of large, well-designed studies assessing healthy behavior and pharmacologic interventions in adults to prevent the progression from IGT to diabetes have been published. No pharmacologic agent is currently approved for diabetes prevention in Canada. Recently, more data has emerged on the role of bariatric surgery in prevention of type 2 diabetes in high-risk groups; however, the cost-benefit analysis of surgical intervention remains questionable (15).

Healthy Behaviour Interventions

A majority of the randomized controlled trials with healthy behaviour interventions enrolled participants with IGT based on OGTT results. However, as the use of OGTT is diminishing clinically for screening for prediabetes and diabetes, and alternative methods including glycated hemoglobin (A1C) and fasting plasma glucose (FPG) are being used more frequently, the recommendations based on the following randomized controlled trials will be applied to a prediabetes diagnosis, irrespective of the testing method.

Healthy behaviour interventions were assessed in the Finnish Diabetes Prevention Study (DPS) (16) and the Diabetes Prevention Program (DPP) (17). A comprehensive structured program that targeted dietary modification with a low-calorie, low-fat, low-saturated fat, high-fibre diet and moderate-intensity physical activity of at least 150 minutes per week resulted in a moderate weight loss of approximately 5% of initial body weight. In both studies, the risk reduction for diabetes was 58% at 4 years. On the basis of the observed benefits of healthy behaviour interventions in the DPP, all participants were offered further lifestyle interventions for a median of 5.7 more years, and benefits were sustained for up to 10 years in the Diabetes Prevention Program Outcomes Study (DPPOS) (18). In a follow-up analysis of the DPP intensive lifestyle intervention cohort, 2-year weight loss was the strongest predictor of reduced diabetes incidence (19). Weight cycling, defined as the number of 2.25 kg weight cycles, was positively associated with incident diabetes. After adjustment for baseline weight, the effect of weight cycling remained statistically significant for diabetes risk (19). In another follow up of the DPP study, lower weight and plasma glucose level early on at 6 and 12 months strongly predicted lower subsequent diabetes risk with healthy behaviour interventions although the study was not completely blinded (20). In the long-term follow up of the randomized Finnish Diabetes Prevention Study (DPS), similar results were noted over 13 years with respect to decreased incidence in diabetes (20,21).

In another healthy behaviour intervention trial, 458 Japanese males with IGT were randomly assigned in a 4:1 ratio to a standard intervention (n=356) or an intensive intervention (n=102) and followed for 4 years (22). Intensive treatment was associated with a 67.4% reduction in risk of diabetes ($p<0.001$). In a more recent trial, 641 Japanese men (aged 30 to 60 years) with overweight and IFG were randomized to either a frequent intervention group (n=311) or a control group (n=330) for 36 months. The frequent intervention group received individual instruction and follow-up support for healthy behaviour interventions from medical staff 9 times. The control group received similar individual instruction 4 times at 12-month intervals during the same period. Results showed an incidence of type 2 diabetes of 12.2% in the frequent intervention group and 16.6% in the control group, with an adjusted hazard ratio (HR) in the frequent intervention group of 0.56 [95% confidence interval (CI) 0.36–0.87]. Post hoc subgroup analyses showed the HR reduced to 0.41 (95% CI 0.24–0.69) among participants with IGT at baseline and to 0.24 (95% CI 0.12–0.48) among those with a baseline A1C level >5.6% (23).

A 23-year follow up of the Chinese Da Qing Diabetes Prevention Trial showed that after 6 years of active healthy behaviour interventions vs. no treatment, the active group had less diabetes, CV and all-cause mortality. This study enrolled 577 people, 439 of whom were assigned to the intervention group and 138 who were assigned to the control group. A total of 174 participants died during the 23 years of follow up (121 in the intervention group vs. 53 in the control group). Cumulative incidence of CVD mortality was 11.9% (95% CI 8.8–15.0) in the intervention group vs. 19.6% (95% Cl 12.9–26.3) in the control group (HR 0.59, 95% CI 0.36–0.96; p=0.033). All-cause mortality was 28.1% (95% CI 23.9–32.4) vs. 38.4% (HR 0.71, 95% CI 0.51–0.99, p=0.049). Incidence of diabetes was 72.6% vs. 89.9% (HR 0.55, 95% CI 0.40–0.76, p=0.001) (24).

Medical Nutrition Therapy

Nutrition therapy and counselling are essential components of the treatment and management of prediabetes. A prospective randomized parallel group study of 76 adults with IFG (or an A1C of 5.7% to 6.4%) found that individualized medical nutrition therapy (MNT) provided by a registered dietitian significantly decreased A1C in individuals diagnosed with prediabetes, compared with usual care after 12 weeks (5.79% vs. 6.01%) (25). The 12-week intervention consisted of four nutrition visits; self-management training; instruction on a high-carbohydrate (60% to 70% daily calories), high-fibre, low-fat (<7% calories from saturated fat) diet; and weight loss (individualized caloric goals to achieve 0.45 to 0.9 kg/week weight loss to achieve 5% body weight loss).

Dietary Patterns

There is strong evidence to support the use of the Mediterranean diet in diabetes prevention. In 2015, Esposito et al conducted a systematic review of all meta-analyses and randomized controlled trials that compared the Mediterranean diet with a control diet for the treatment of type 2 diabetes and prediabetes. Higher adherence to the Mediterranean diet reduced the risk of future diabetes by 19% to 23% (26). Included in this systematic review is one long-term randomized controlled trial, the PREDIMED trial, in which a subgroup analysis restricted to those without diabetes at baseline found that a Mediterranean diet significantly reduced development of type 2 diabetes during follow up (27). Older individuals (55 to 75 years of age) living in Spain with high risk of CVD were

randomized to 1 of 3 interventions: Mediterranean diet supplemented with extra virgin olive oil (EVOO) (50 mL/day), Mediterranean diet supplemented with mixed nuts (30 g/day) or a control diet consisting of advice to reduce intake of all types of fat. After a median 4.8-year follow up, a statistically significant 40% relative risk reduction and a non-significant 18% risk reduction in diabetes risk was seen in the Mediterranean diet groups supplemented with EVOO and mixed nuts, respectively, in comparison with the control group. The beneficial effect was attributed to the overall composition of the dietary pattern, and not to calorie restriction, increased physical activity or weight loss because these healthy behaviour interventions were not part of the intervention and between-group changes were negligible.

In addition to the Mediterranean diet, a significant reduction of type 2 diabetes has also been found to be associated with healthy dietary patterns, including the DASH (Dietary Approaches to Stop Hypertension) diet, the AHEI (Alternate Healthy Eating Index) and various other healthy dietary patterns, derived by factor or cluster analysis (28). A meta-analysis of 18 prospective studies from 20 cohorts in four world regions demonstrated that adherence to these healthy diets are consistently associated with a 20% reduced risk of future type 2 diabetes (28). While the nature of diets associated with prevention of type 2 diabetes may vary, these healthy diets share several common components, including whole grains, fruit, vegetables, nuts, legumes, olive oil, white meat/seafood, little or moderate alcohol, reduced intake of red and processed meats and sugar-sweetened beverages.

Diets Emphasizing Specific Foods

Increased consumption of whole grains and dairy products have shown promising results with respect to decreased incidence of type 2 diabetes.

Whole grains

A large prospective cohort of postmenopausal women from the Women's Health Initiative Observational Study demonstrated that the consumption of whole grains was inversely associated with incident type 2 diabetes over a median 7.9 years of follow up (29). Adjusted for age and energy intake per day, successively increasing categories of whole grain consumption were associated with significant reduced risk of developing type 2 diabetes. Women who consumed greater than 2 servings of whole grains per day had a 43% reduced risk of incident type 2 diabetes compared with women who consumed no whole grain (29).

Dairy

A meta-analysis of 17 cohort studies (30) reported an inverse association between intakes of total dairy, low-fat dairy products and cheese and risk of type 2 diabetes (30). Nonlinear inverse associations were observed for total dairy products and yogurt, with most of the benefit being observed when increasing the intake of total dairy products from little to no dairy up to 300 to 400 g/day or yogurt up to 120 to 140 g/day, above which there was no further benefit. The associations between low-fat dairy products and cheese and type 2 diabetes were borderline nonlinear ($p \leq 0.06$), with most of the benefit observed when increasing the intake of these items up to 300 to 400 g/day for low-fat dairy, and up to ~50 g/day for cheese.

Physical Activity

Higher levels of leisure time physical activity (LTPA) are associated with substantially lower incidence of type 2 diabetes (31). A systematic review and dose-response meta-analysis which included over one million individuals from 28 prospective cohort studies provided information on the association between LTPA (24 cohorts) or total physical activity (4 cohorts) and incidence of type 2 diabetes (31). The results suggested a curvilinear relationship and found a risk reduction of 26% for type 2 diabetes (31) among those who achieved 11.25 metabolic equivalents (MET) h/week (equivalent to 150 minutes per week of moderate activity). Individuals who attained twice this amount of physical activity were associated with a risk reduction of 36%, with even further risk reductions, 53%, at a higher dose of 60 MET/week. The greatest relative benefits were attained at low levels of activity, but further benefits can be recognized at levels that go well beyond those prescribed by the current minimum recommendation of 150 minutes per week of moderate intense activity. Similarly, the 25-year cohort Coronary Artery Risk Development in Young Adults (CARDIA) study measured fitness in 4,373 participants from young adulthood to middle age and found that fitness was associated with a lower risk for developing prediabetes and type 2 diabetes, even when adjusting for body mass index (BMI) over this time period (32). Future research is needed to consider the dose-response relationship of physical activity and type 2 diabetes prevention in ethnically diverse populations.

Pharmacotherapy

Metformin

Metformin was used in a second randomized arm of the DPP and compared to lifestyle and to placebo (17). A dosage of 850 mg twice daily for an average of 2.8 years significantly decreased progression to diabetes by 31% compared to placebo. An analysis of the subgroup with FPG 6.1 to 6.9 mmol/L showed a 48% reduction in diabetes diagnosis. In the DPP population, metformin did not have a significant effect in the older age group (>60 years) and in subjects with less obesity (BMI <35 kg/m^2). Among women reporting a history of GDM, both intensive healthy behaviour interventions and metformin therapy reduced the incidence of diabetes by approximately 50% compared with the placebo group, whereas this reduction was 49% and 14%, respectively in parous women without GDM (33). These data suggest that metformin may be more effective in women with a history of GDM as compared with those without. To determine whether the observed benefit was a transient pharmacological effect or was more sustained, a repeat OGTT was undertaken after a short washout period. The results of this study suggested that 26% of the diabetes prevention effect could be accounted for by the pharmacologic action of metformin (which did not persist when the drug was stopped). After the washout, the incidence of diabetes was still reduced by 25% (34). The benefits of metformin on diabetes prevention persisted for up to 10 years (18).

A subsequent analysis of DPP that analyzed diabetes incidence defined by A1C ≥6.5% found a 44% reduction by metformin and 49% by healthy behaviour interventions during the DPP, and by 38% by metformin and 29% by healthy behaviour interventions over 10 years of follow up (35). Unlike the primary DPP and DPPOS findings based on glucose criteria, metformin and healthy behaviour interventions were similarly effective in preventing diabetes defined by A1C. Additionally, there was a significant interaction ($p<0.01$) between baseline A1C and the effects of healthy behaviour interventions and metformin treatment were greater at higher baseline A1C between 6.0% to 6.4% range, compared to lower A1C baseline categories.

Overall, metformin may be considered as a strategy to prevent type 2 diabetes in people with IGT (especially in combination with IFG or with elevated A1C between 6.0% to 6.4% range). Metformin may be more effective among younger individuals (<60 years) with significant obesity (>35 kg/m^2) and among women with a history of GDM.

Thiazolidinediones

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial randomized 5,269 people with IGT and/or IFG, in a 2 x 2 factorial fashion, to ramipril (up to 15 mg/ day) and/or rosiglitazone (8 mg/day) vs. placebo (36,37). Eligible subjects were >30 years of age and not known to have CVD. The primary outcome of DREAM was a composite of development of diabetes or death. Treatment with rosiglitazone resulted in a 60% reduction in the primary composite outcome of diabetes or death (HR 0.40, 95% CI 0.35–0.46), primarily due to a 62% relative reduction in the risk of progression to diabetes (HR 0.38, 95% CI 0.33–0.44). In the Actos Now for the Prevention of Diabetes (ACT NOW) study, 602 high-risk participants with IGT were randomized to receive pioglitazone or placebo and were followed for 2.4 years. Pioglitazone decreased the conversion of IGT to type 2 diabetes by 72% ($p<0.00001$) (38). In the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) trial, the combination of metformin 500 mg twice daily and rosiglitazone 2 mg twice daily was found to reduce the progression to diabetes by 66% (95% CI 41–80) among 103 people with IGT compared to 104 people randomized to placebo over a median of 3.9 years (39).

Recently, the Insulin Resistance Intervention after Stroke (IRIS) trial demonstrated that pioglitazone reduced the development of type 2 diabetes by 52% over 4.8 years along with also reducing stroke and myocardial infarction (MI) after a recent ischemic stroke or transient ischemic attack (TIA) in people with insulin resistance and prediabetes (40). A total of 3,876 people with recent ischemic stroke or TIA, no history of diabetes, FPG <7.0 mmol/L and insulin resistance by homeostasis model assessment of insulin resistance (HOMA-IR) score >3.0 were randomly assigned to pioglitazone or placebo. Surveillance for diabetes onset during the trial was accomplished by periodic interviews and annual FPG testing. At baseline, the mean FPG, A1C, insulin and HOMA-IR were 5.46 mmol/L, 5.8%, 22.4 mIU/mL, and 5.4, respectively. After 1 year, mean HOMA-IR and FPG decreased to 4.1 and 5.3 mmol/L in the pioglitazone group and rose to 5.7 and 5.5 mmol/L in the placebo group (all $p<0.0001$). Over a median follow up of 4.8 years, diabetes developed in 73 (3.8%) participants assigned to pioglitazone compared with 149 (7.7%) assigned to placebo (HR 0.48, 95% CI 0.33–0.69, $p<0.0001$). This effect was predominantly driven by those with initial IFG (FPG >5.6 mmol/L; HR 0.41, 95% CI 0.30–0.57) or elevated A1C (>5.7%, HR 0.46, 95% CI 0.34–0.62]). The study did not provide information whether this effect would be sustained. Other limitations include reduction in type 2 diabetes not being the primary outcome measure, poor adherence, no washout of study drug and some people likely already had diabetes at study entry.

Despite the favourable effects of thiazolidinediones on delaying the development of type 2 diabetes, the multiple potential adverse effects and warnings in this class of medication make it difficult to recommend their widespread use in people with IFG or IGT.

Acarbose

The Study to Prevent Non-Insulin Dependent Diabetes (STOP-NIDDM) used acarbose at a dosage of 100 mg three times a day in a 5-year study with a mean follow up of 3.3 years (41). Overall, there was a 25% reduction in the risk of progression to diabetes when the diagnosis was based on one OGTT and a 36% reduction in the risk of progression to diabetes when the diagnosis was based on two consecutive OGTTs. However, when the acarbose was discontinued, the effect did not persist (41). In another trial, 1,780 Japanese people with IGT were randomly assigned to oral voglibose 0.2 mg three times a day (n=897) or placebo (n=883) (42). Results showed that, over a mean of 48.1 weeks, voglibose was more effective than placebo at reducing the progression to type 2 diabetes (5.6% vs. 11.9%, HR 0.595, 95% CI 0.433–0.818, p=0.0014). More subjects in the voglibose group achieved normoglycemia than in the placebo group (66.8% vs. 51.5%, HR 1.539, 95% CI 1.357–1.746, $p<0.0001$).

Orlistat

The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study examined the effect of orlistat in combination with an intensive lifestyle modification program (diet and exercise) on the prevention of diabetes in 3,305 individuals with obesity (43). Subjects were randomized to orlistat 120 mg or placebo three times a day with meals for 4 years. Weight loss was observed in both groups, but the orlistat group lost significantly more (5.8 vs. 3 kg, $p<0.001$). Compared to placebo, orlistat treatment was associated with a further 37% reduction in the incidence of diabetes. However, two important methodological limitations affect the interpretation of these results. First, there was a very high dropout rate of 48% in the orlistat group and 66% in the placebo group. Second, the last observation carried forward was used for analysis, which is generally not favoured for prevention or survival studies.

Liraglutide

Liraglutide has been shown to prevent IGT conversion to type 2 diabetes and cause reversion to normoglycemia (44). In a 20-week study, liraglutide was administered to 564 individuals with obesity who did not have diabetes, 31% of whom had IGT. Subjects were randomized to 1 of 4 liraglutide doses (1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg, n=90–95) or to placebo (n=98), or to orlistat (120 mg, n=95) three times daily. A1C was reduced by 0.14% to 0.24%. The prevalence of prediabetes decreased by 84% to 96% with liraglutide 1.8 mg, 2.4 mg and 3.0 mg doses. In a secondary outcome analysis from another randomized trial of 56 weeks duration among 3,731 participants with obesity who did not have type 2 diabetes (61% participants with IGT and remaining participants with normoglycemia at baseline), 4 participants in the liraglutide 3.0 mg group and 14 in the placebo group developed diabetes ($p<0.01$) (45).

Recently, in a 3-year extension study of the Satiety and Clinical Adiposity — Liraglutide Evidence in Nondiabetic and Diabetic Individuals (SCALE) Obesity and Prediabetes study, adults with prediabetes and a body mass index of at least 30 kg/m^2, or at least 27 kg/m^2 with comorbidities, were randomized 2:1, using a telephone or web-based system, to once-daily subcutaneous liraglutide 3.0 mg (n=1,505) or placebo (n=749), as an adjunct to a reduced-calorie diet and increased physical activity to determine the conversion from prediabetes to overt type 2 diabetes (46). One thousand one hundred and twenty-eight (50%) completed the study up to week 160, after withdrawal of 714 (47%) in the liraglutide group and 412 (55%) in the placebo group. By week 160 (about 3 years), 26 (2%) of 1,472 in the liraglutide group vs. 46 (6%) of 738 in the placebo group were diagnosed with diabetes while on treatment, which was the primary outcome. The mean time from randomization to diagnosis was 99 weeks (SD 47) for the 26 in the liraglutide group vs. 87 weeks (SD 47) for the 46 in the placebo group who were diagnosed with diabetes. Taking the different diagnosis frequencies between the treatment groups into account, the time to onset of diabetes over 160 weeks among all randomized was 2.7 times longer with liraglutide than with placebo (95% CI 1.9 to 3·9, $p<0·0001$), corresponding with a HR of 0.21, 95% CI 0.13–0.34. Liraglutide induced greater weight loss than placebo at week 160 [–6.1% (SD 7.3) vs. –1.9% (SD 6.3)]; estimated treatment difference –4.3% (95% CI –4.9 to –3.7, $p<0.0001$). Serious adverse events were reported by 227 (15%) of the 1,501 randomized in the liraglutide group vs. 96 (13%) of 747 in the placebo group. The limitations included the fact that withdrawn individuals were not followed up after discontinuation, cost effectiveness

of the active therapy compared to healthy behaviour interventions alone and questionable long-term adverse effects.

Vitamin D

A systematic review and meta-analysis compared vitamin D3 supplementation with placebo or a non-vitamin D supplement in adults with normal glucose tolerance, prediabetes, or type 2 diabetes (47). Thirty-five trials (43,407 participants) with variable risk of bias were included. Vitamin D had no significant effects on insulin resistance [homeostasis model assessment of insulin resistance: MD –0.04; 95% CI -0.30 to 0.22, I-squared statistic (I^2)=45%], insulin secretion (homeostasis model of beta-cell function: MD 1.64, 95% CI –25.94 to 29.22, I^2=40%), or A1C (MD –0.05%, 95% CI –0.12 to 0.03, I^2=55%) compared with controls. Definitive conclusions may be limited in the context of the moderate degree of heterogeneity, variable risk of bias, and short-term follow-up duration of the available evidence to date.

Bariatric Surgery

A systematic review and meta-analysis consisting of 18 studies (43,669 participants, 30,774 with IGT and/or IFG), looking at people with obesity at risk for type 2 diabetes (BMI >30 kg/m^2) showed an odds ratio 0.10 (0.02–0.49) with bariatric surgery for diabetes diagnosis. Many limitations exist in this paper, including not all subjects being randomized and biases in publication (15). Additionally, the cost-benefit analysis for bariatric surgery as a primary tool to prevent diabetes is unclear. Hence, more data is needed before recommending bariatric surgery routinely to prevent diabetes.

Diabetes Prevention in High-Risk Ethnicities

Certain ethnic groups, including African, Arab, Asian, Hispanic, Indigenous and South Asian peoples, are at very high risk for and have a high prevalence of type 2 diabetes (12% to 15% in the Western world) (48,49). The reasons for this are multifactorial and include genetic susceptibility, altered fat distribution (more visceral fat with greater insulin resistance) and higher prevalence of metabolic syndrome. Many of them develop diabetes at a younger age and often have complications at the time of diagnosis due to long-standing, pre-existing diabetes. As a result, there may be a benefit of delaying the onset of diabetes in this population. The Indian Diabetes Prevention Programme randomized 531 people with IGT diabetes in Chennai, India to 4 groups: healthy behaviour interventions; metformin; healthy behaviour interventions and metformin; and control with a median follow up of 30 months. Progression to diabetes in the control group was high (55%) over 3 years (50). The relative risk reduction was 28.5% with healthy behaviour interventions, 26.4% with metformin and 28.2% with healthy behaviour interventions and metformin compared with the control group.

Another study utilizing a stepwise approach of healthy behaviour interventions with the option of adding metformin reduced the risk of type 2 diabetes in Asian Indian adults (51). This was a randomized, controlled trial of 578 Asian Indian adults with overweight or obesity with isolated IGT, isolated IFG, or IFG and IGT in Chennai, India. Participants were randomized to standard lifestyle advice (control) or a 6-month, culturally tailored, United States Diabetes Prevention Program-based lifestyle curriculum, plus stepwise addition of metformin (500 mg twice daily) for participants at highest risk of conversion to diabetes at 4+ months of follow up, defined as having either IFG+IGT or IFG and A1C ≥5.7%. The primary outcome of diabetes incidence was assessed biannually and compared across study arms using an intention-to-treat analysis. During 3 years of follow up, 34.9% of control and 25.7% of intervention participants developed diabetes (p=0.014); the relative risk reduction (RRR) was 32% (95% CI 7–50), and the number needed to treat to prevent one case of diabetes was 9.8. The RRR varied by prediabetes type and was only significant for IFG and IGT (RRR =36%), although the magnitude was similar but non-significant for isolated IGT (RRR =31%). Among subgroups, RRR was stronger in participants 50 years or older, male, or with obesity. Most participants (72.0%) required metformin in addition to healthy behaviour interventions, although there was variability by prediabetes type (isolated IFG, 76.5%; IFG and IGT, 83.0%; isolated IGT, 51.3%). Limitations included lack of power for subgroup comparisons, simplistic assessment of physical activity, and potential for lack of generalizability since the population was Asian Indian only.

The above approach of stepwise prevention intervention may lead to cost savings, fewer complications and lower morbidity, but it remains to be proven with hard clinical endpoints. Healthy behaviour interventions not only reduce the risk of diabetes but have other health benefits, so the overall benefit is positive with little harm. One must keep in mind that the measures of prevention must be delivered in a culturally sensitive manner to these populations.

Population Level Interventions for Prevention of Type 2 Diabetes

At a macro-level, the type 2 diabetes epidemic has been attributed to urbanization and environmental transitions, including sedentary occupations, increased mechanization, improved transportation, as well as increased accessibility to unhealthy diets with high-calorie content and large portion sizes. In recent decades, men and women around the globe (and in Canada) have gained weight, largely due to changes in dietary patterns and decreased physical activity levels. The dominant effect of obesity in precipitating glucose intolerance and its consequences suggests that reversal of the diabetes epidemic can only come about with urgent and substantial changes to health behaviours on a population level. It is important to recognize that the health sector on its own cannot accomplish population-wide changes. New strategic relationships with groups that have an impact on health (e.g. food industry and construction industry) are needed to help create an environment more conducive to an active lifestyle and healthy eating habits.

Major legislative and other regulatory measures may be required similar to those needed to address illness arising from tobacco usage. Some examples of this are transformation of work environment, development of school curriculum to improve physical and nutritional education, improvement of food labelling on packaged foods, mandating nutrition labelling of restaurant foods and regulating advertisements, especially to children, etc. In addition, food choices may be influenced by price increases (taxation) or price decreases (subsidies). In a recent systematic review and meta-analysis (52), a 10% price subsidy increased consumption of healthy foods by 12% (95% CI 10±15%), including intake of fruits and vegetables by 14% (95% CI 11±17%); whereas a 10% increase in price decreased consumption of unhealthy foods by 6% (95% CI 4±8%), including sugar-sweetened beverage intake by 7% (95% CI 3±10%). Greater intake of sugar-sweetened beverages has been associated with higher type 2 diabetes risk in a meta-analysis (53) and a pooled analysis of European cohorts (54). This association remains significant even after adjusting for BMI, suggesting that the deleterious effects of sugar-sweetened beverages on diabetes are not entirely mediated by body weight. Diabetes Canada has a public health advocacy campaign recommending (i) limited intake of free sugars to <10% of total daily calorie intake, and (ii) limited intake of sugar-sweetened beverages.

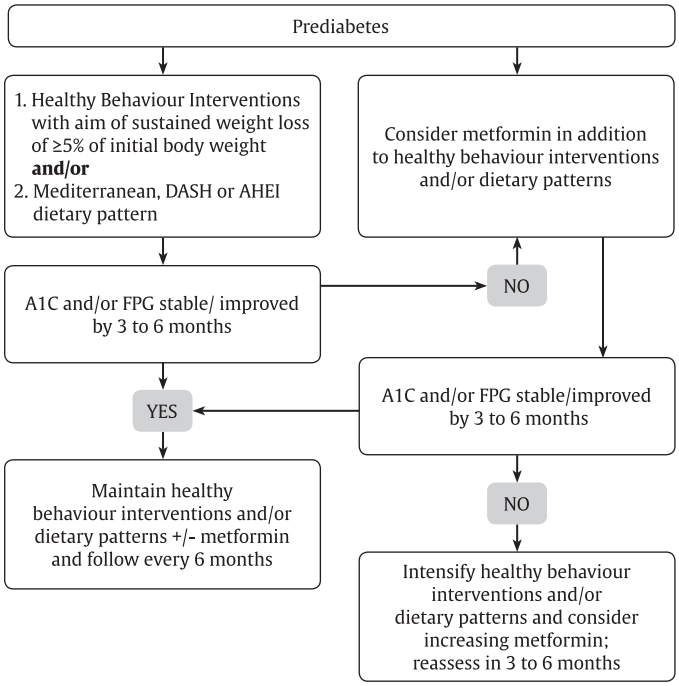

Figure 1. Flowchart for reducing the risk of type 2 diabetes.
A1C, glycated hemoglobin; *AHEI*, Alternate Healthy Eating Index; *DASH*, Dietary Approaches to Stop Hypertension; *FPG*, fasting plasma glucose.

RECOMMENDATIONS

1. In individuals with prediabetes, a structured program of healthy behaviour interventions that includes moderate weight loss and regular physical activity of a minimum of 150 minutes per week over 5 days a week should be implemented to reduce the risk of type 2 diabetes [Grade A, Level 1A (16,17) for individuals with IGT; Grade B, Level 2 [23] for individuals with IFG; Grade D, Consensus for individuals with A1C 6.0%–6.4%].

2. In individuals at risk for type 2 diabetes, dietary patterns may be used to reduce the risk of diabetes, specifically:
   a. Mediterranean-style [Grade C, Level 3 (26)]
   b. DASH (Dietary Approaches to Stop Hypertension) [Grade C, Level 3 (28)]
   c. AHEI (Alternate Healthy Eating Index) [Grade C, Level 3 (28)].

3. In individuals with prediabetes, pharmacologic therapy with metformin may be used to reduce the risk of type 2 diabetes [Grade A, Level 1A (17,33) for individuals with IGT; Grade D, Consensus for individuals with IFG or A1C 6.0%–6.4%].

Abbreviations:
A1C, glycated hemoglobin; *BMI*, body mass index; *CI*, confidence interval; *CV*, cardiovascular; *CVD*, cardiovascular disease; EVOO, extra virgin olive oil; *GDM*, gestational diabetes; *HR*, hazard ratio; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance.

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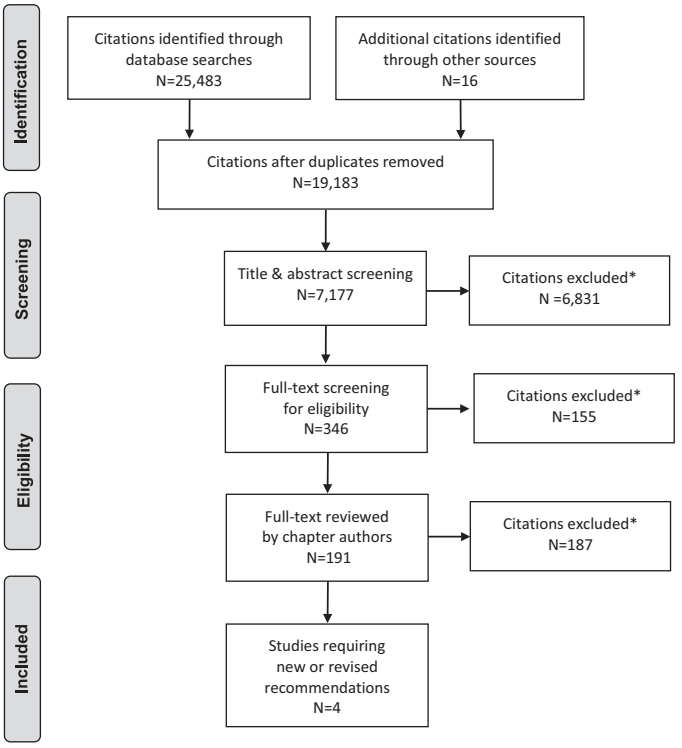
Literature Review Flow Diagram for Chapter 5: Reducing the Risk of Developing Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design

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2018 Clinical Practice Guidelines

Organization of Diabetes Care

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes care should be:
  - Organized around the person living with diabetes and their supports. The person with diabetes should be an active participant in their own care, be involved in shared-care decision making and self-manage to their full abilities.
  - Facilitated by a proactive, interprofessional team with training in diabetes and the ability to provide ongoing self-management education and support.
  - Organized within the context of the expanded chronic care model and delivered using as many of the components of the model as possible (in particular, self-management education and support; interprofessional team-based care with expansion of professional roles; collaboration with the primary care provider and monitoring with medication adjustment and case management).
  - Structured, evidence based and supported by clinical information and decision support systems that include patient registries, clinician and patient reminders, facilitated relay of information, audits, feedback and benchmarking.
- Any of the above strategies may be facilitated with telehealth technologies.

KEY MESSAGES FOR PEOPLE LIVING WITH DIABETES

- Know the members of your diabetes team and stay connected with them.
- Remember you are the most important member of the team.
- Be prepared to learn how to care for your diabetes on a daily basis. Also, be ready to share in decision making regarding how you will care for your diabetes and health.
- Prepare for visits with your diabetes health-care team:
  - Have laboratory tests done prior to the visit so the results will be available to review at the visit.
  - Be prepared to set and update your personal goals for caring for your diabetes and health. Be prepared to share any issues that may affect your ability to care for your diabetes on a daily basis, including any fears or anxiety you may have.
  - Bring your medication bottles or an up-to-date medication list, including nonprescription drugs and supplements. Also, bring your glucose meter and insulin pen device if you use one.
  - Bring or upload your most recent glucose monitoring results as well as other health behaviour records (e.g. food and exercise diary), as well as a health-care diary in which you have recorded important health events (e.g. visits with health-care providers, surgeries, illnesses, vaccinations).
- Share the information you learn during your visits with your diabetes health-care team with all of your health-care providers and diabetes team members.
- If travel distance or time is a barrier to your care, ask your team about telehealth (telephone, web-based or virtual) diabetes support and visits.

HELPFUL HINTS BOX: ORGANIZATION OF CARE

Recognize: Consider diabetes risk factors for all of your patients and screen appropriately for diabetes.
Register: Develop a registry for all of your patients with diabetes to track care.
Resource: Support self-management through the use of interprofessional teams, which could include the primary care provider, diabetes educator, registered dietitian, nurse, pharmacist, specialists and self-management supports, including linkage to community services.
Relay: Facilitate information sharing between the person with diabetes and the health-care team for coordinated care and timely management changes.
Recall: Develop a system to remind your patients and caregivers of timely review and reassessment.

Introduction

In Canada, there is a care gap between the clinical goals outlined in evidence-based guidelines for diabetes management and actual clinical practice (1,2). Since almost 80% of the medical care of people with diabetes takes place in primary care, there has been a growing recognition that the redesign of this practice setting needs to focus on inclusion of the 6 essential components of the chronic care model (CCM) (3–6). The CCM provides an organizational framework that identifies the essential components of the system, practice and community that encourage high-quality chronic disease care and creates quality-improvement (QI) opportunities to guide practice redesign to meet these evidence-based components. These components facilitate planning and coordination among health-care providers while helping people with diabetes play an informed and active role in managing their own care (7).

QI is an interprofessional, systems-focused, data-driven method of understanding and improving the efficiency, effectiveness and reliability of health processes and outcomes of care (8). Although self-management with the support of the interprofessional diabetes health-care team is integral to diabetes care, evidence suggests that the CCM, which includes components beyond the person with diabetes and health-care provider, provides a useful framework for the

Conflict of interest statements can be found on page S33.

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optimal care of persons with diabetes (6,7,9–12). This chapter reflects the importance of the CCM design, delivery and organization of diabetes care. To assist the readers in increasing their understanding and application of the CCM framework in their daily practice, the terminology and QI strategies have been re-organized under the 4 main components of the CCM (Table 1).

The chronic care model and organization of diabetes care

In many ways, optimal diabetes care delivery reflects the essential components of the CCM (Figure 1). This model aims to transform the care of people with chronic illnesses from acute and reactive to proactive, planned and population-based. Early studies have shown that the following interventions improved care in the chronically ill: educating and supporting the patient; team-based care; increasing the health-care provider's skills and use of registry-based information systems (9,10,13). The current CCM has expanded on this evidence to include the following 6 components that work together to strengthen the provider-patient relationship and improve health outcomes: 1) delivery system design; 2) self-management support; 3) decision support; 4) clinical information systems; 5) the community; and 6) health systems.

Systematic reviews have found that primary care practices are able to successfully implement the CCM (6,7). Furthermore, incorporating most or all of the CCM components has been associated with improved quality of care and disease outcomes in people with various chronic illnesses, including diabetes (6,7,10,12–16). A systematic review and meta-analysis of QI strategies on the management of diabetes concluded that interventions targeting the system of chronic disease management, along with patient-mediated QI strategies, should be an important component of interventions aimed at improving care. Although some of the improvements were modest, it may be that, when the QI components are used together in a multifaceted approach, there is a synergistic and additive effect, as noted in the above studies (11,12,17–19).

CCM in Diabetes

Review of the various CCM components and their effectiveness indicate that the more components reflected in the practice, the better the outcomes [see multi-component QI initiatives] (10,12,15,18–21). Organizations that provide diabetes care in accordance with the CCM provide better quality care than organizations that were less likely to use components of this model (22). Furthermore, the degree to which care delivered in a primary care setting conforms to the CCM has been shown to be an important predictor of the 10-year risk of coronary heart disease (CHD) in people with type 2 diabetes (23). Initially, it appeared as if only process outcomes, such as behaviours of patients and caregivers, are improved with the CCM; however, with longer-term use of the model in clinical practice, improvements in other outcomes were noted, such as reductions in glycated hemoglobin (A1C) and low-density lipoprotein cholesterol (LDL-C) levels (12,24). A large, 2-arm, cluster-randomized QI trial, using all 6 dimensions of the CCM, found significant improvements in A1C and LDL-C and an increase in the use of statins and antiplatelet therapy among people with diabetes (5). A meta-analysis of randomized controlled trials assessing the effectiveness of disease management programs for improving glycemic control found significant reductions in A1C with programs that included the fundamental elements of the CCM (25). Other trials found that use of the CCM improved cardiovascular (CV) risk factors in people with diabetes (23,26). One large-scale analysis of a nationwide disease management program, using the CCM and based in primary care, reduced overall mortality as well as drug and hospital costs (27).

A recent systematic review of which type of QI intervention improves outcomes noted that the percentage of studies that have used all 4 components of the CCM has risen from 29% to 57% from those published before 2003 to those published up to 2011. Like other reviews, this review found that the more components used from the CCM, the better the outcomes (12,18,19,28). The Assessment of Chronic Illness Care (ACIC) is a practical assessment as well as a research tool that can help health-care teams strategically involve themselves in a structured way to assess and identify gaps to develop into a more robust CCM (29).

Components of the CCM that Improve Care

Delivery system design

The team. The most important member of the diabetes health-care team is the person living with diabetes. Current evidence continues to support the importance of a multidisciplinary and interprofessional team with specific training in diabetes within the primary care setting (13,17,25). The team should work collaboratively with the primary care provider, or ideally have primary care imbedded in the team. These health-care providers should be supported by a diabetes specialist, with this support being either direct as an interdisciplinary team member, or indirect through shared care or educational support (5,17,30). In adults with type 2 diabetes, this care model has been associated with improvements in A1C, blood pressure (BP), lipids and care processes compared to care that is delivered by a specialist or primary care physician alone (5,30–34). Community-based intermediate care clinics, led by a specialist nurse and supported by a consultant or primary care physician specially trained in diabetes, achieved significant improvements in glycemic control, BP and LDL-cholesterol in people with poorly controlled type 2 diabetes compared to routine primary care. The odds of achieving all 3 targets was 1.5 times greater in the intervention group, but statistically was marginally insignificant (30). A reduction in preventable, diabetes-related emergency room visits also has been noted when the team includes a nurse trained in diabetes care who follows detailed treatment algorithms (32). In Canada, observational data from primary care networks, whose approach is to improve access and coordinate care, suggest that patients who are part of interprofessional teams have better outcomes and fewer hospital visits than patients who are not (35,36).

Team membership beyond physicians may be extensive and should include disciplines that have been shown to improve a variety of clinical outcomes, including nurses (33,37–40), nurse practitioners (41), dietitians (42), pharmacists (43–45) and providers of psychological support (46). Diabetes educators, of any health-care profession, continue to be integral members of the team. A systematic review (33) and meta-analysis (37) found that case management led by specialist nurses or dietitians improved both glycemic control and CV risk factors. Another study found improved BP outcomes with nurse-led interventions vs. usual care, particularly when nurses followed algorithms and were able to prescribe (38). In addition, a large randomized controlled trial found that nurse-led, guideline-based, collaborative-care management was associated with improvements in A1C, lipids, BP and depression in people with depression and type 2 diabetes and/or CHD (39,40). Practices with nurse practitioners were also found to have better diabetes process measures than those with physicians alone or those employing only physician assistants (41). Small-group or individualized nutrition counselling by a registered dietitian with expertise in diabetes management is another important element of team-based care. A variety of individual and community health-care support systems, particularly psychological support, can also improve glycemic control (46).

Table 1
Definition of terms (13,17,21,29,85)

Chronic care model (CCM)	The CCM is an organizational approach to caring for people with chronic diseases as well as a quality-improvement strategy, the components of which are evidence based. These components facilitate planning and coordination among providers, while helping people play an informed role in managing their own care. This model has evolved from the Wagner original (1999) to the Expanded Care Model (85).
Components of CCM	• Delivery system design • Self-management support • Decision support • Clinical information • The community • Health systems
Quality-improvement strategies	A multidisciplinary, systems-focused, data-driven method of understanding and improving the efficiency, effectiveness and reliability of health processes and outcomes of care.

Components of CCM	**Definitions/examples of subcomponent**
Delivery system design Making systematic changes to primary care practices and health systems to improve the quality, efficiency and effectiveness of patient care.	**Case management** A structured, multifaceted intervention that supports the practitioner/patient relationship and plan of care; emphasizes prevention of exacerbations and complications utilizing evidence-based practice guidelines and patient empowerment strategies. May include education, coaching, treatment adjustment, monitoring and care coordination, often by a nurse, pharmacist or dietitian. **Structured care** Regular clinical follow up using evidence-based guidelines. **Shared care** Joint participation of primary care provider [first contact and ongoing health care: family physician, general practitioner or nurse practitioner] and specialty care physician in the planned delivery of care, informed by an enhanced information exchange over and above routine discharge and referral notices. Shared care can also refer to the sharing of responsibility for care between the person with diabetes and provider or team. **Team changes** Changes to the structure of a primary health-care team, such as adding a team member or shared care, such as a physician, nurse specialist or pharmacist, using an interprofessional team in primary routine management, expansion of professional role (e.g. nurse or pharmacist has a more active role in monitoring or adjusting medications). **Team-based care** Care by a multidisciplinary and interprofessional team with specific training in diabetes. **Continuous quality improvement** Techniques for examining and measuring clinical processes, designing interventions, testing their impacts and then assessing the need for further improvement.
Self-management support Self-management support is defined as activities that support the implementation and maintenance of behaviours for ongoing diabetes self-management. Such activities may include education, behaviour modification, psychosocial and/or clinical support, including internal and community resources, such as disease management programs with patient reminders, monitoring and feedback, and peer-led support/interest groups.	**Self-management education** A systematic intervention that involves active participation by the person with diabetes in self-monitoring (physiologic processes) and/or decision making (managing). See Self-Management Education and Support chapter, p. S36). **Patient education** General and disease specific.
Decision support Integration of evidence-based guidelines into the flow of clinical practice.	**Audit and feedback** Summary of provider or group performance on clinical or process indicators delivered to clinicians to increase awareness of performance. **Benchmarking** Feedback on the performance of a person with diabetes or physician, which is ranked against that of a peer group. **Clinician education** May include didactic, academic detailing, online, customized cases with feedback. **Evidence–based guidelines** Adherence to guidelines may be facilitated by embedding into electronic medical records with reminders (see below) or with the use of clinical flow sheets.
Clinical information systems The part of an information system that helps organize patient and population data to facilitate efficient and effective care. May provide timely reminders for providers and patients, identify relevant sub-populations for proactive care, facilitate individual patient care planning, share information with patients and providers to coordinate care or monitor performance of practice team and care system.	**Clinician reminders** Paper-based or electronic system to prompt health-care professionals to recall patient-specific information (e.g. A1C) or do a specific task (e.g. foot exam). **Electronic medical records** **Facilitated relay of information to clinician** Clinical information collected from patients and sent to clinicians, by means other than the existing medical record (e.g. electronic or web-based methods) through which the patient provides self-care data. In general, most effective when the person receiving the information has prescribing, ordering or medication-adjusting abilities. In general, the person with diabetes should be facilitating the relay but may come from other team members. **Patient registry** A list of people sharing a common characteristic, such as diabetes. May be paper-based, but increasingly is electronic, from a simple spreadsheet to one embedded in an electronic health record. Allows for recording and tracking of care. **Patient reminders** Any effort to remind people about upcoming appointments or aspects of self-care (e.g. glucose monitoring).

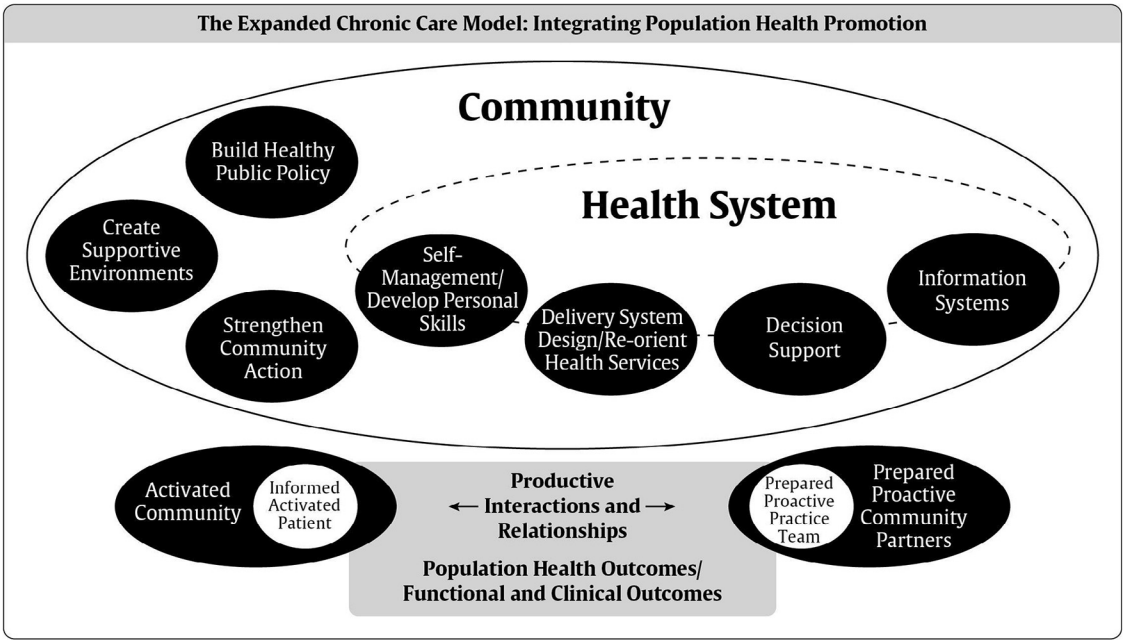

Figure 1. The expanded chronic care model: integrating population health promotion. Used with permission from reference 85.

A meta-analysis involving people with both type 1 and type 2 diabetes showed a significant 0.76% decrease in A1C (47) as well as improved adherence and quality of life (QOL) and reductions in adverse drug reactions and LDL-C with collaborative pharmacist intervention (43). A Canadian randomized trial that added a pharmacist to primary care teams showed a significant reduction in BP for people with type 2 diabetes (44). A systematic review of pharmacist-led disease management found resource use was generally the same as usual care, improved medication use and adherence and attainment of clinical goals such as A1C, BP and LDL-C (45).

Roles within the team and case management. Flexibility in the operation of the team is important. Team changes, such as adding a team member, active participation of professionals from more than 1 discipline and role expansion, have been associated with improved clinical outcomes (13,17,25,48). The greatest body of evidence for improved clinical outcomes in diabetes is with promotion of self-management, team changes and case management (5,13,17,25,34,48–50). A systematic review and meta-analysis of QI strategies showed that the application of the following QI strategies improved outcomes, such as A1C, BP and cholesterol, as well as process outcomes, medication use and screening for complications: promotion of self-management, team changes, case management, education of the person with diabetes, facilitated relay, electronic patient registries, patient reminders, audits and feedback, and clinician reminders (17) (Table 1). The effectiveness of different QI strategies may vary based on the baseline A1C with QI targeting clinicians only beneficial when the baseline A1C control is poor (17). In practice, many of these QI strategies occur in concert with one another through the use of interprofessional teams. Another recent systematic review showed that education of the person with diabetes, support and provider role changes, along with telehealth, are the QIs most associated with improvements in glycemic and CV risk factor control (48).

Another meta-analysis that defined case management as using at least 2 of the following 5 components—patient education, coaching, treatment adjustment (where the manager is able to start or modify treatment with or without prior approval from the primary care physician), monitoring, care coordination (where the manager reminds the person with diabetes about upcoming appointments or important aspects of self-care and informs the physician about complications, treatment adjustments or therapeutic recommendations)—found that a high frequency of contact with the person with diabetes and the ability of a case manager to start or modify treatment with or without prior approval from the primary care physician had the greatest impact on A1C lowering. Case management programs also were more effective for people with poor glycemic control (A1C >8%) at baseline (25). Another recent review of systematic reviews and randomized trials using nurse case managers found that the more advanced the skills from training and experience, the better the outcomes compared to primary care nurses with minimal training. Furthermore, the outcomes when these nurse case managers were used was equivalent or better than primary care providers (40). Other disease management strategies that have been associated with positive outcomes are the delegation of prescribing authority and the monitoring of complications using decision support tools (33,34,38).

The primary care provider, who is usually a family physician, has a unique role on the team, particularly with regard to providing continuity of care. They are often the principal medical contact for the person with diabetes and have a comprehensive overview of all health issues and social supports (51). Within primary care, there is some evidence that group medical visits may be effective in improving glycemic control (52,53).

Some people with diabetes require ongoing, specialized care, such as children, emerging adults (age 14 to 29 years) and pregnant women (54–60). There is also evidence that specialized care may be more beneficial in people with type 1 diabetes (61,62). In the CCM, collaborative, shared care is the ideal approach to organizing care for individuals with diabetes. Collaborative care for adults with depression and type 2 diabetes, largely in the form of nurse-led case management, in short-to-medium term, has shown significant improvement in both depression and glycemic outcomes (63). A recent population-based study showed that early endocrinologist care among medically complex people with diabetes was associated with a lower incidence of CV events and all-cause death (64). Studies have supported the shared care model (65) and have shown

that specialist input into specialized diabetes teams at the interface of primary and secondary care improves outcomes (5,30,66).

Self-management support

Self-management support (SMS) is an umbrella term used by the CCM model, which includes self-management education, and is the cornerstone of diabetes care in the CCM, enabling the person with diabetes to take a more active role in problem solving and personalized goal setting (17,48) (see Self-Management Education and Support chapter, p. S36).

Decision support

Decision support or a clinical decision support system (CDSS), which provides health-care practitioners with best-practice information at the point of care to help support decision making, has been shown to improve outcomes. Evidence-based guideline interventions, particularly those that used interactive computer technology to provide recommendations and immediate feedback of personally tailored information, were shown to be the most effective in improving outcomes of people with diabetes (67). A randomized trial using electronic medical record (EMR) decision support in primary care found improvement in A1C (68), and a cluster randomized trial of a QI program found that the provision of a clear treatment protocol—supported by tailored postgraduate education of the primary care physician and case management support by an endocrinologist—substantially improved the overall quality of diabetes care provided, as well as major diabetes-related outcomes (66). Incorporation of evidence-based treatment algorithms has been shown in several studies to be an integral part of diabetes case management (13,33,38,41). The use of simple decision support tools, such as clinical flow sheets, has been associated with improved adherence to clinical practice guidelines (69). Clinical outcomes improve with CDSS when combined with both feedback and case management; for example, insulin adjustment algorithms for people with type 2 diabetes (18,70,71). Audits and feedback lead to improvements in professional practice (72). This is particularly effective when combined with benchmarking (73).

Clinical information systems

Clinical information systems (CIS) that allow for a population-based approach to diabetes assessment and management, such as electronic health (medical) records (EMRs) and electronic patient registries, have been shown to have a positive impact on evidence-based diabetes care (17,29,74–78). Practice-level clinical registries give an overview of an entire practice, which may assist in the delivery and monitoring of patient care. In addition to providing clinical information at the time of a patient encounter, CIS can also help promote timely management and reduce the tendency toward clinical inertia (79). Provincial and national registries are also essential for benchmarking, tracking diabetes trends, determining the effect of QI programs and resource planning. A large study based on observational data support the premise that federal policies in the United States encouraging the meaningful use of EMRs, may improve the quality of diabetes care, with sites using EMRs achieving better outcomes than those that were paper-based (78). Another study showed that, among people with diabetes, the use of an outpatient EMR was associated with a reduction of emergency visits and hospitalizations (80).

Physician and patient reminders, which generally require a CIS, have also shown benefit (17,66). Patient reminders can include interventions that facilitate scheduling, attendance or availability to provider of patient information integral to the visit (e.g. self-monitoring of blood glucose [SMBG]). In a systematic review, interventions of benefit were, for scheduling: phone calls, letters, text and patient portal; for attendance: letter, phone calls, SMS, email reminders, and financial incentives; and for visit information: web-based programs (case management), phone calls, SMS, mail reminders, decision support systems linked to guidelines, and registries integrated with EMR and health records (76). Facilitated relay of information to clinicians, which has been shown to improve care, may include electronic or web-based methods through which people with diabetes provide self-care data for the clinician to review. Generally, it is the person with diabetes who is facilitating the relay. Ideally, this should occur in case management with a team member who has prescribing or ordering authority (17,76).

Community

Environmental factors, such as food and housing security, the ability to lead an active lifestyle, as well as access to care and social supports, also impact diabetes outcomes. Community partnerships should be considered as a means of obtaining better care for people with diabetes. For example, in addition to the diabetes health-care team, peer- or lay leader-led self-management groups have been shown to be beneficial in persons with type 2 diabetes (83,84).

Health systems

Support for diabetes care at the level of the health-care system, such as the national and provincial systems, is essential. A number of provinces have adopted an expanded CCM (85) that includes health promotion and disease prevention (86). Many provinces and health regions also have developed diabetes strategies, diabetes service frameworks and support diabetes collaboratives. Some trials on diabetes-specific collaboratives have been shown to improve clinical outcomes (26,66,87).

Provider incentives represent another area of health system support. Some provinces have added incentive billing codes for the care of people with diabetes so that health-care providers can be financially compensated for the use of evidence-based flow sheets as well as time spent collaborating with the person with diabetes for disease planning (88). Pay-for-performance programs, which encourage the achievement of goals through reimbursement, are more commonly used outside of Canada. To date, these programs have had mixed results (89–91). A recent review of systematic reviews of QI strategies stated that they were unable to find any high-quality systematic reviews on financial incentives and the quality of diabetes care (48). Various payment systems have been studied, but it is still unclear which of these improve diabetes outcomes (92,93). Incentives to physicians to enroll people with diabetes and provide care within a nationwide disease management program appear to improve quality of care (27), as does infrastructure incentive payments that encourage the CCM (16). A meta-analysis that included physician incentives as a QI has shown mixed results for improved outcomes. Capitation payments and the addition of team-based care has shown moderate improvements in processes related to diabetes care (94); however, pay-for-performance programs introduced in the United Kingdom had limited effect on outcomes (17,95).

Multicomponent Quality Improvement Initiatives

Many studies of QI have used multiple strategies (17). Those that intervened on the entire system of chronic disease management produced the greatest effect (e.g. case management, team changes, registries, facilitated relay, continuous QI) and were not dependent on starting A1C. A number of reviews have attempted to determine which QI interventions have the best evidence for improved

outcomes (12,18,19). Systematic reviews suggest that multifaceted interventions, using a variety of clinicians in a structured way with organizational support, yield the best results (12,18,19). One review that looked specifically at interventions aimed at primary care providers described multiple component interventions as those ranging from "electronic coaching, staff training, algorithm-driven care, reminders, alerts and audits all in different combinations to the targeting of multidisciplinary teams, including case managers, general practitioners, pharmacists, community health workers and dietitians." This analysis did not show as much benefit when targeting the health professionals alone. Educational interventions to physicians alone did not yield any positive results but, when delivered as interactive education with simulated participants and feedback, decreased A1C (18). One review showed mixed results for pharmacists, with improvement in A1C seen when the pharmacist intervention was multicomponent, including: counselling, patient education, telephone coaching, management and regular reviews to support SMBG, adherence support and reminders of checks for diabetes complications (18).

A meta-analysis of QIs found to be of benefit in rural areas, showed only 20% of the interventions that included a single strategy had high impact on improvement of self-management, while this increased to 80% with 2 strategies and to 100% of those including 3 strategies or more ($p<0.05$) (19). The same trend was seen with clinical outcomes with 10% effective if 1 strategy, 20% if 2 and 50% if 3 or more.

Structured care typically includes multiple QI interventions. For example, the Diabetes Care in General Practice (DCGP) study, with 19 years of follow up, was a multicentre, cluster-randomized 6-year trial using a multitude of QI with SMS in the form of goal setting, clinical information with registries and regular follow up, decision support in the use of guidelines, delivery system design with the use of interprofessional teams with feedback and medical education, and showed a decrease in all diabetes-related endpoints, fatal and nonfatal MIs (81). The Diabetes Shared Care Program was a retrospective cohort study of 120,000 people with diabetes randomly assigned to an integrated model of care that used multicomponent QIs vs. usual care and demonstrated a lower risk of CV events, stroke and all-cause mortality in the intervention group (82).

Telehealth

Telehealth (also called telemedicine or telecare) is the provision of health care remotely by means of a variety of telecommunication tools, including telephones, smartphones and mobile wireless devices, with or without a video connection (96). Although not a specific component of the CCM, telehealth technologies may help facilitate many of the QI strategies (97). In case management, the frequency of contact has been shown to be important and telehealth may facilitate this (25). This may be particularly beneficial in rural settings with limited access (19,98). A mixed systematic review that looked at quantitative as well as qualitative studies in telehealth showed that telehealth technologies in type 2 diabetes produce a variety of outcomes, including improved health status, such as reduced A1C, increased quality of care (guideline adherence), decreased health service use cost and increased patient satisfaction and knowledge. This review defined the multiple telehealth technologies from simple interventions (e.g. telemonitoring) to more complex (97) (Table 2). No single technology appears to be superior, but tailoring of the technology for the patient and implementation, as well as user interface, appears to improve adoption and outcomes (96,97). Another systematic review of information technology found that telehealth in both type 1 and type 2 diabetes populations is a more effective intervention in reducing A1C compared with other information technology strategies (99). Two other systematic reviews and meta-analysis of randomized controlled trials involving both type 1 and type 2 showed meaningful reduction in A1C (100,101). In general, A1C improvement is most likely to occur when telehealth systems allow for medication adjustment (100). Another review found the effect on A1C to be greater in type 2 and argued that this was because the average age was higher and benefited from increased frequency of remote monitoring (101,102). It made no difference if the intervention had been done by the nurse or physician (103). There was a trend of a decreasing effect in glycemic control over time, suggesting that contact with the person with diabetes may need to intensify to minimize a trend of decreasing intervention impact over time. As with many other QI strategies, improvement in glycemic control when using telehealth was better when the starting A1C was higher (>8.0%) (103,104).

Social networking services (SNS) which allow the user to set up an online profile and interact with a defined list of other users, thereby engaging with an online community, has been shown in a meta-analysis of randomized controlled trials to improve glycemic control (105). SNS has not typically been included in telehealth, but these studies present a novel way of using SNS to include direct access to a health-care professional and real-time feedback. This review found SNS more effective when compared to usual care in improving systolic and diastolic BP, triglycerides (TG) and total cholesterol and, particularly in type 2 diabetes, reducing A1C. This may be because SNS is better suited to target modifiable lifestyle risk factors, which are more associated with type 2 diabetes. Systematic reviews have found that telehealth is 1 of 3 QI strategies with consistent evidence for improvement in glycemia and CV risk factors in people with diabetes (48). In addition to telemonitoring of health data, such as glucose readings or BP and disease management, telehealth technologies may be used for conferencing or education of team members and teleconsultation with specialists. Benefits are noted regardless of whether the teleconsultation is asynchronous or synchronous (106,107).

Table 2
Examples of Telehealth Interventions and Technologies used in Diabetes Care*

Simple Interventions
Telemonitoring
Telediagnosis / consultation
Complex Interventions
Telemonitoriing +/- e-learning, telediagnosis, SNS
Telehealth Technology Used
Single technology-direct transmission, smart phone, teleconference (phone or video) website-internet, pager, personal digital assistant
Multiple technologies-direct transmission +/- smart phone, teleconference, website, internet
Users of Telehealth Technologies
Persons with diabetes +/- nurses, physicians, nutritionist, other specialists
Physicians +/- eye care technicians

SNS, social networking services.
* Adapted from reference 97.

RECOMMENDATIONS

1. Diabetes care should:
   a. Be organized around the person living with diabetes (and their supports). The person living with diabetes should be an active participant in their own care and shared-care decision making; and self-manage to their full abilities; and

b. Be facilitated by a proactive, interprofessional team with specific training in diabetes. The team should be able to provide ongoing self-management education and support, and incorporate as many components of the CCM as possible [Grade A, Level 1A (11,12) for type 2 diabetes; Grade C, Level 3 (27) for type 1 diabetes for both (a) and (b)].

2. The following quality-improvement strategies should be used alone or in combination to reduce A1C and improve 1 or more of the following: BP, LDL-C, adherence to recommended diabetes complication screening:
   a. Promotion of self-management [Grade A, Level 1A (17,48)]
   b. Team changes [Grade A, Level 1A (17,48)]
   c. Case management [Grade A, Level 1A (17,25,76)]
   d. Patient education [Grade A, Level 1A (17,48)]
   e. Facilitated relay of clinical information [Grade A, Level 1A (17,76)]
   f. Electronic patient registries [Grade A, Level 1A (17,76)]
   g. Patient reminders [Grade A, Level 1A (17,76)]
   h. Audit and feedback/benchmarking [Grade A, Level 1A (17,73)]
   i. Clinician education [Grade A, Level 1A (17,18)]
   j. Clinician reminders (with or without decision support) [Grade A, Level 1A (17,70)]
   k. Clinical decision support systems (processes of care only and clinical outcomes when combined with feedback, case management) [Grade A, Level 1A (70,71)]
   l. Structured care [Grade A, Level 1A (12,81)]
   m. Multicomponent QI strategies [Grade A, Level 1A (12,18,19)].

3. An interprofessional team with specific training in diabetes and supported by specialist input should be integrated within diabetes care delivery models in the primary care [Grade A, Level 1A (17,25)] and specialist care [Grade D, Consensus] settings.

4. The role of the diabetes case manager should be enhanced, in cooperation with the collaborating physician [Grade A, Level 1A (17,25)], to include interventions led by a nurse [Grade A, Level 1A (37,38,40)], pharmacist [Grade B, Level 2 (45,47)] or registered dietitian [Grade B, Level 2 (42)] to improve coordination of care and facilitate timely changes to diabetes management.

5. The following individuals should work with an interprofessional team with specialized training in these areas of diabetes as part of a collaborative, shared care approach:
   a. Children with diabetes [Grade D, Level 4 (54)]
   b. Adolescents and emerging adults (age 14–29 years) with type 1 diabetes as part of a structured transitional program [Grade C, Level 3 (108)]
   c. People with type 1 diabetes [Grade C, Level 3 (61)]
   d. Women with pre-existing diabetes who require preconception counselling and prenatal counselling [Grade C, Level 3 (55–57,59,60) and women with gestational diabetes [Grade D, Consensus].

6. Referral to an interprofessional team with specialized training may be considered for:
   a. Individuals with type 2 diabetes who are consistently not meeting cardiometabolic targets [Grade A, Level 1 (30)]
   b. Adults with depression and diabetes for collaborative care and, in particular, nurse case management for improvement in depression and glycemic control [Grade A, Level 1A (63)].

7. Telehealth technologies may be used to:
   a. Improve self-management in underserviced communities [Grade B, Level 2 (98)]
   b. Facilitate consultation with specialized teams as part of a shared-care model [Grade A, Level 1A (106)]
   c. Improve clinical outcomes in type 2 diabetes, including a decrease in A1C, an increase in quality of care (i.e. guideline adherence), a decrease in health service use and cost, and an increase in patient satisfaction and knowledge [Grade A, Level 1A (97,103,105)]
   d. Improve glycemic and CV risk factor control in type 1 and type 2 diabetes [Grade A, Level 1 (100,101,103)].

Abbreviations:
A1C, glycated hemoglobin; *BMI*, body mass index; *BP*, blood pressure; *CCM*, chronic care model; *CV*, cardiovascular disease; *LDL-C*, low-density lipoprotein; *QOL*, quality of life; *SMBG*, self-monitoring of blood glucose; *SNS*, social networking services.

Other Relevant Guidelines

Self-Management Education and Support, p. S36
Diabetes and Mental Health p. S130
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255
Type 2 Diabetes and Indigenous Peoples, p. S296

Relevant Appendix

Appendix 3. Sample Diabetes Patient Care Flow Sheet for Adults

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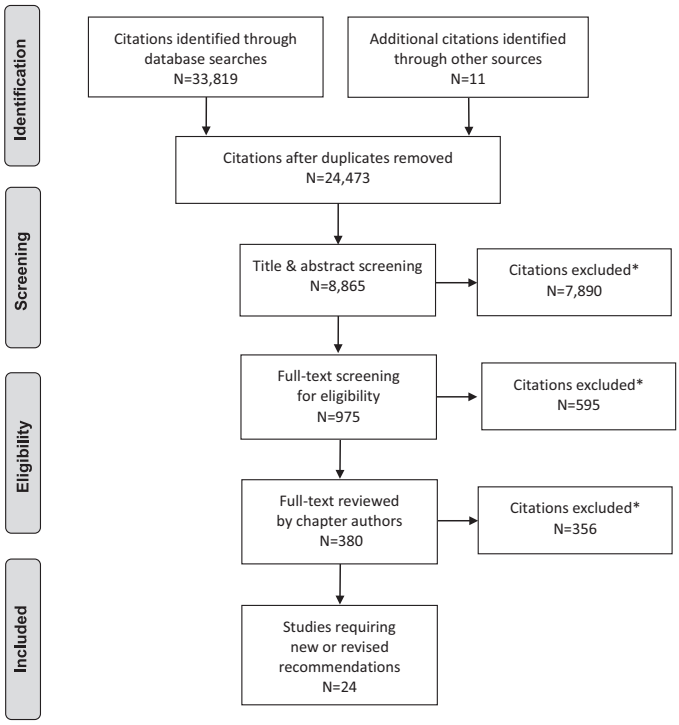
Literature Review Flow Diagram for Chapter 6: Organization of Diabetes Care



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Self-Management Education and Support

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Offer collaborative and interactive self-management education and support.
- Incorporate problem solving, goal setting and self-monitoring of health parameters for ongoing self-management of clinical and psychosocial aspects of care.
- Design and implement person-centred learning to facilitate informed decision-making and achievement of individual goals.
- Individualize self-management education interventions according to the type of diabetes and recommended therapy within the context of the individual's ability for learning and change, culture, health beliefs and preferences, literacy level, socioeconomic status and other health challenges.
- Create and offer self-management support that reflects person-centred goals and needs.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- A variety of diabetes education and support programs are available to you. These may include group classes and individual counselling sessions, as well as strategies that use technology (e.g. Internet-based computer programs, mobile phone apps).
- You are strongly encouraged to access diabetes self-management education and support when you are first diagnosed, as well as during times when there are changes in your diabetes treatment, general health or life circumstances.
- Work with your diabetes team to:
  - Establish a trusting and collaborative relationship
  - Set goals for caring for your diabetes and health, and
  - Identify strategies to help you manage your diabetes.

Introduction

The dynamic nature of diabetes and its impact on multiple aspects of one's life requires individuals to make frequent and ongoing self-management decisions. Therefore, the title of this chapter has been modified to include self-management education (SME) and self-management support (SMS), in recognition of the growing evidence and benefit of SMS for individuals living with diabetes, particularly when combined with SME (1).

SME is a process to facilitate individuals in decision-making, resulting in improvements in variables, such as knowledge, attitudes and self-efficacy, as well as improvements in healthy behaviours and clinical outcomes (2). SME is defined as a systematic intervention that involves active participation by the individual in self–monitoring of health parameters and/or decision-making with the application of knowledge and skills (3). It also recognizes that patient-provider collaboration, approaches and the development of problem-solving skills are crucial for sustained self-care (4). SMS includes activities that support the implementation and maintenance of behaviours for ongoing diabetes self-management, including education, behaviour modification, psychosocial and/or clinical support (5,6). The goal of SME and SMS is to foster opportunities for people with diabetes to become informed and motivated to continually engage in effective diabetes self-management practices and behaviours. To date, a growing body of research evidence indicates that the combination of both SME and SMS is most advantageous for improving glycemic control, self-efficacy, self-care behaviours (i.e. monitoring of blood glucose and healthy eating) and reducing diabetes distress and foot complications (1,6).

Self-Management Education

Several meta-analyses have demonstrated that SME is associated with clinically important benefits in people with diabetes, such as reductions in glycated hemoglobin (A1C) (1,3,7–11) and improvements in cardiovascular (CV) risk factors and reductions in foot ulcerations, infections and amputations (1). A large population-based cohort study of 27,278 people with type 2 diabetes and no known previous cardiovascular disease (CVD) found that attending structured diabetes education was associated with a reduction in: all-cause mortality of 44%, first CVD episode of 20% and stroke of 30% (12). A large retrospective cohort study of 26,790 individuals who had had at least 1 diabetes education session demonstrated lower diabetes-related health-care expenditures after 12 months compared to individuals who did not receive diabetes education (13). Improved quality of life has also been demonstrated (14), in addition to sustained weight loss and CV fitness for up to 4 years following education (15). SME also improved short- and long-term (1 year) self-efficacy and reduced diabetes-related stress (16).

Defining SME

Diabetes SME has evolved from traditional didactic teaching to a variety of educational, psychological and behavioural interventions, and collaborative teaching methods, tailored to the individual's specific needs (17). SME comprises any educational processes that provide individuals with the knowledge and skills to inform decisions and increase their capacity and confidence to apply these

Conflict of interest statements can be found on page S40.

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skills in daily life situations (4). Interventions and strategies for ongoing self-management of medical, behavioural and emotional aspects of care may be integrated into knowledge and technical skills training (1).

A review of 18 systematic reviews found that educational interventions that emphasize knowledge, emotional and behaviour support, coping strategies and self-management training were associated with improved glycemic control at all ages (1). Additionally, SME strategies that incorporate individual goal setting (16), collaboration, problem solving (18), patient empowerment strategies (12) and tailored education (1) were effective in improving glycemic control and self-care outcomes for individuals with diabetes. Furthermore, SME results in positive changes in diabetes-related knowledge (19), as well as psychological (20–23) and behavioural (20,24) domains. Basic knowledge and skills for SME include monitoring of relevant health parameters, healthy eating, physical activity, pharmacotherapy, prevention and management of hypo- and hyperglycemia, and prevention and surveillance of complications. Skill training includes self-monitoring of blood glucose (SMBG); making healthy dietary choices; incorporating physical activity; stress management; and medication adherence and adjustment (25,26).

Finally, research demonstrates that combining complex cognitive and affective (emotional) interventions to support the detection of problems, identify possible causes and generate corrective actions, were most effective in improving glycemic control (27). The acquisition of knowledge may be augmented with cognitive behavioural interventions to achieve longer-term change in self-care behaviours (7,20,22,28). These include cognitive restructuring, problem solving, cognitive behavioural therapy (CBT), stress management, goal setting and relaxation techniques. All of these recognize that personal awareness and alteration of causative (possibly unconscious) thoughts and emotions are essential for effective behaviour change (29).

Cognitive behavioural interventions share common elements, including a patient-centred approach, shared decision-making, the development of problem-solving skills, and the use of action plans directed toward patient-chosen goals, (20,22,30) and may be used in both individual and group settings (17,20). In general, group settings are more effective for short-term glycemic control, whereas group interventions combined with individual follow-up sessions result in lower glycated hemoglobin (A1C) levels than either setting alone (31). Cognitive-behavioural interventions are effective in lowering A1C (8,32,33), improving quality of life (34,35) and increasing self-care behaviours (20,32), although other studies show mixed results (7,28). A meta-analysis of behavioural interventions for type 1 diabetes found a reduction in A1C of –0.29% after 6 months (9). A network meta-analysis found that 11 or more hours of behavioural interventions for type 2 diabetes were associated with a reduction of A1C of at least 0.4%. The reduction in A1C was even greater in those with baseline A1C levels greater than 7.0%, in adults less than 65 years of age, and in visible minority populations (10). Interventions that combine strategies for knowledge acquisition and self-care management (22,28) appear to be more effective in increasing knowledge, self-efficacy and self-care behaviours and in achieving metabolic control than didactic and knowledge-oriented programs alone (8,17,32,36).

Delivering diabetes SME

Diabetes SME is based on a trusting and collaborative patient-health-care professional relationship (6,8). A growing number of studies demonstrate that early diabetes SME is effective in improving glycemic control (1). However, statistically and clinically significant improvements in A1C were seldom maintained after 3 months without additional SMS (1). Frequent communication is key for successful interventions, whether by an interprofessional, in-hospital diabetes team or a community setting (37,38). Effective individual health-care provider communication may improve adherence by decreasing barriers to overall diabetes management (39).

Many systematic reviews demonstrate that access to an interprofessional team for diabetes education is associated with improvements in glycemic control, lipids and blood pressure (BP) (1). Diabetes education interventions that used a combination of health-care professionals (diabetes educators) were more successful in improving glycemic control for individuals with type 2 diabetes (–1.84%) than interventions that used nurse only (–0.80) or non-nursing personnel (–0.77%) (40). However, nurses working in combination with other health-care professionals are most effective in decreasing A1C levels (–1.84%) (40). Furthermore, expanding the role of educators, to include medication management, support and monitoring of individuals with diabetes, is associated with improvements in glycemic control, cholesterol and BP (1).

Evidence on the use of new technology to support SME in diabetes is still emerging. The current literature suggests that virtual environments provide a feasible and useful platform for diabetes education and support for people with diabetes as well as educators (41,42). SME delivered via the Internet is effective at improving measures of glycemic control and diabetes knowledge in adults with type 2 diabetes compared with usual care (1,41). Internet-delivered diabetes education may increase access for many individuals and they can engage in self-paced learning. The ability to interact with or message an educator/health-care provider is an attractive option to individuals (41); however, most studies report that Internet/web usage declines over time (2,41). New online materials may need to be added for ongoing engagement (41). The use of interactive modules that allow for tracking and tailored feedback, the addition of personalized components from counselors or peer supporters, and/or emails and telephone contacts allow for, and contribute to, the development of online communities (42).

A meta-analysis of computer-based diabetes self-management interventions (via clinics, the Internet and mobile phone apps) to manage type 2 diabetes appears to have a small beneficial effect on A1C (–0.2%), and this effect was larger in the mobile phone subgroup (–0.5%) (43). However, there was no evidence of benefit for other biological, cognitive, behavioural or emotional outcomes (43). Mobile applications, especially text messaging, may also be used as educational tools for improving outcome among people with type 2 diabetes (2,44). In a meta-analysis of 13 trials, a difference in A1C of 0.53% was reported in the intervention compared to usual care. The acceptability of such approaches are mixed as some report high satisfaction, while others report participants requesting to stop the messages before the end of the intervention, and low acceptability for challenging interfaces or inexperienced participants with mobile web use (2). Age, diabetes duration, A1C, and type and length of the intervention may also have implications on the effectiveness of such approaches (44).

Tailoring SME

The content and skill-training components of SME are most effective when individualized according to: the type of diabetes and recommended therapy; the individual's ability for learning and readiness for change; the context of one's cultural beliefs, health beliefs and preferences; literacy level; socioeconomic barriers and other health challenges (8,31,45). Tailoring SME to the individual is paramount. All trials evaluating a culturally appropriate education module (incorporating cultural or faith traditions, values and beliefs, delivery in the person's preferred language, adapted cultural dietary advice, the person's needs and/or involving family members) note improvements in diabetes-related knowledge, self-management behaviours and clinical outcomes (46,47). Family and culturally tailored interventions are particularly relevant

in minority communities. Several randomized controlled trials and systematic reviews demonstrate that culturally competent health-care interventions result in lower A1C levels and improvements in diabetes-related knowledge and quality of life (34,37,48). Family and social support positively impact metabolic control and self-care behaviours (37,48,49). In both type 1 and type 2 diabetes, interventions that target the family's ability to cope with stress result in fewer conflicts, and having partners involved in care positively impacts glycemic control (49).

Reviews and meta-analyses conclude that culturally appropriate health education for type 2 diabetes has short-to-medium term effects on glycemic control (mean reduction of A1C ranging from –0.2% to –0.5%) up to 24 months and improved scores on knowledge of diabetes and healthy behaviours for up to 6 months (47,50). Studies identifying program characteristics associated with greater success for minority populations show larger reductions in A1C with individual and face-to-face delivered educational programs and peer educators, than with group-based diabetes education programming (46,51). Additionally, content and materials geared toward people with low literacy and numeracy can be successful in improving outcomes, such as A1C, self-efficacy and BP (52). Training health-care professionals about health literacy, numeracy and clear communication principles to address low literacy can also be effective (53,54).

Finally, self-identification of problems or need for self-care improvement by the individual is critical to all cognitive-behavioural interventions (32,55). The health-care provider's role is to collaboratively facilitate this awareness or identification of issues (4). Standardized instruments, such as knowledge questionnaires, the Problem Areas in Diabetes (PAID) (56), Diabetes Self-Efficacy (DSE) (16), Self-care Inventory-Revised (SCI-R 2005) (57), or Summary of Diabetes Self-Care Activities (58) may have value in this process (59), although they have been used mainly for research purposes.

Self-Management Support

SMS (also addressed in the Organization of Care chapter, p. S27) refers to policies and people that support self-management behaviours across the lifespan, and are not necessarily specific to educational processes. There is growing evidence that short-term benefits of SME can be further sustained with SMS (1,6). Although historically, diabetes educators have provided SMS, educators are increasingly challenged to offer and maintain SMS, such as frequent and ongoing supportive follow up and case management due to expanding caseloads, complexity of individual diabetes care and limited time and resources (6).

Defining SMS

Diabetes SMS is defined as strategies that augment an individual's ability to self-manage their diabetes (6). Such support may include frequent follow up by a health-care provider, diabetes coaching, peer support or community health workers, linkages with community support groups or interest groups. To date, a growing body of research evidence indicates that combining SME and SMS is most advantageous for improving glycemic control, self-efficacy and self-care behaviours, and reducing diabetes distress and foot complications (1,6,16).

Delivering SMS

The availability of several different technologies, including the Internet, web-based education and communities, text messaging (60–64), email, automatic telephone reminders (65) and telehealth/telephone education (66–69) provide an effective and time-efficient means of providing SMS. Although the delivery strategy for SMS appears to be dependent on the population and context, evidence suggests that frequent interactions with text message systems on mobile phones when combined with the Internet to relay blood glucose records are associated with improved glycemic control (1,43,44,70). Additional systematic reviews of healthy behaviour programs for those living with type 2 diabetes found that web-based programs are effective in increasing physical activity (43,71), decreasing dietary fat intake (43) and improving overall dietary intake (42). Finally, several small trials demonstrate improved outcomes when utilizing reminder systems and scheduled follow ups compared to controls. Outcomes include improving SMBG (60,65,71,72), improved adherence to treatment algorithms (73), improved self-efficacy (6,66–68) and quality of life (74), as well as improved clinical outcomes, including reductions in A1C (61–64,67,70,75,76) and weight (69,77).

Peer facilitators may augment multidisciplinary team practices and SME in providing SMS. Studies of peer support show a significant reduction in A1C by –0.57% with individual-based interventions providing the greatest A1C reduction (–0.91%) compared to group or individual and group combined (78). The superiority of peer-delivered programs over similar programs delivered by health professionals is yet to be demonstrated in general populations with type 2 diabetes (79,80). Studies of the incremental effect of peer educators show variability in terms of behaviour change and clinical outcomes (81,82). Although training and scope of practice of peer leaders or community support workers is not clearly articulated in the literature, some examples exist for which the role has been successfully created, implemented and evaluated in clinical and community settings (78,83).

Tailoring SMS

An SMS intervention that is most readily available for tailoring includes frequent follow up with a diabetes educator (84). A telephone-based support intervention (4 phone calls in one year), following education, to reach a lower-income minority population living with diabetes, found that participants who receive telephone contact have an A1C 0.9% lower than those who did not, suggesting that a telephone intervention by diabetes nurse educators is a clinically effective strategy to support diverse populations living with diabetes (84).

Community health workers may also play an important role in tailoring SMS interventions to ethnically diverse populations. A systematic review found that access to a community health worker in a minority population results in a decrease in A1C of –0.37% to –0.75%, with the greatest improvement in A1C at 3 months (83). Peer support and community health workers may offer SMS and engage with individuals with diabetes in the community setting, primarily in faith-based settings, community health centres and at community events (83).

Finally, diabetes coaching is emerging as a promising SMS intervention that offers opportunities for personalized support, depending on an individual's self-management needs and preferences. A recent systematic review identified the coaching role as comprised of goal setting, knowledge acquisition, individualized care and frequent/ongoing follow up (85). The review found that access to diabetes coaching led to a reduction in A1C of –0.32% when offered with usual care over a period of 3 months to 1 year (85); however, the training and regulatory requirements for diabetes coaches have not been clarified, and significant variations in scope of practice remain in the Canadian health-care setting.

Conclusions

Evidence supports the beneficial effect of SME on diabetes clinical, emotional and behavioural outcomes. Increasingly, multifaceted

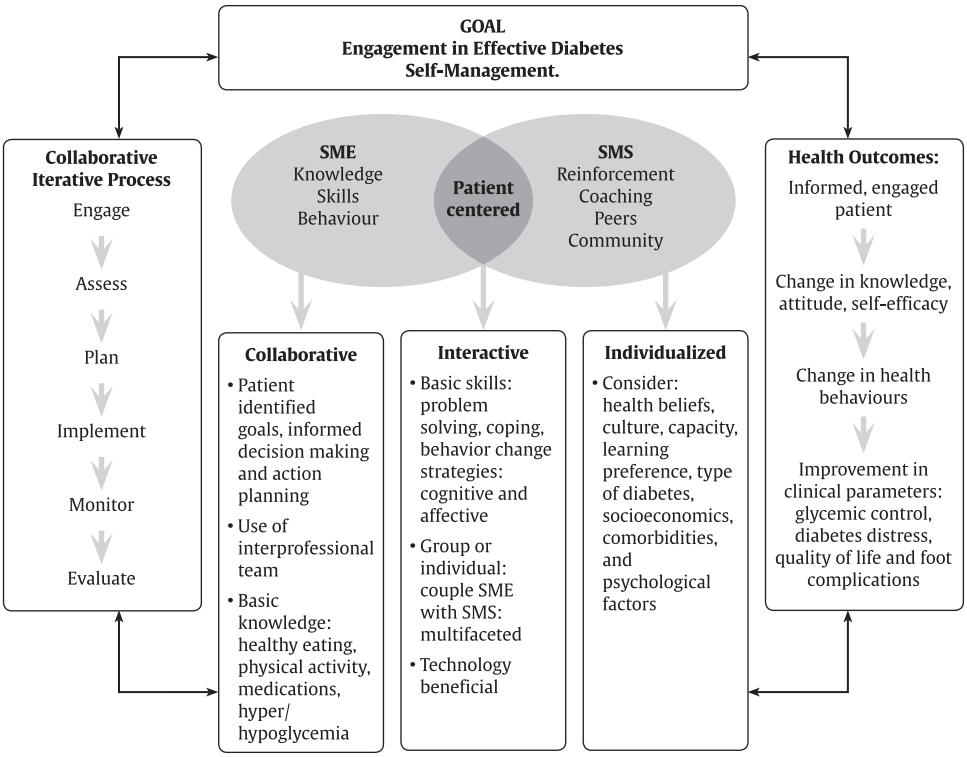

Figure 1. A model for self-management education (SME) and self-management support (SMS).

programs that incorporate behavioural/psychosocial interventions, as well as knowledge and skills training are more effective than didactic educational programs or programs which focus on single strategies (1,7,9,10,17,45). Furthermore, SMS, when coupled with SME, is complementary and sustains the short-term benefits seen with SME (1,6). Interventions that include face-to-face delivery, a cognitive-behavioural method and the practical application of content are more likely to improve glycemic control (33,45,86). The most effective behavioural interventions involve a patient-centred approach, shared decision-making, the development of problem solving skills and the use of action plans directed toward patient-chosen goals (Figure 1).

RECOMMENDATIONS

1. People with diabetes should be offered timely SME that is tailored to enhance self-care practices and behaviours [Grade A, Level 1A (1,7,9,10,38,45)].

2. All people with diabetes who are able should be taught how to self-manage their diabetes [Grade B, Level 2 (16,38,40)].

3. SME that incorporates cognitive-behavioural educational interventions, such as problem solving, goal setting, self-monitoring of health parameters and dietary modifications and physical activity, should be implemented for all able individuals with diabetes [Grade B, Level 2 (18,20,33,42,45,71,86,87)].

4. SME interventions may be offered in small group and/or one-on-one settings [Grade A, Level 1A (88,89) for type 2 diabetes; Grade D, Consensus for type 1 diabetes].

5. Interventions that increase participation and collaboration of the person with diabetes in health-care decision-making should be used by health-care providers [Grade B, Level 2 (38)].

6. Support for self-management should be offered to assist individuals in implementing and maintaining diabetes self-management [Grade B, Level 2 (1)] by offering any of the following:
   a) Peer-led support or community support workers [Grade B, Level 2 (6,78,83)]
   b) Diabetes coaching [Grade B, Level 2 (85)]
   c) Telephone follow up [Grade B, Level 2 (84)].

7. In both type 1 and type 2 diabetes, interventions that target the family's ability to cope with stress or diabetes-related conflict should be included in educational interventions when indicated [Grade B, Level 2 (49)].

8. Technologies, such as Internet-based computer programs and glucose monitoring systems, brief text messages and mobile apps, may be used to support self-management in order to improve glycemic control [Grade A, Level 1A (44,70) for type 2 diabetes; Grade B, Level 2 (1) for type 1 diabetes].

9. Culturally appropriate SME and SMS, which may include peer or lay educators, may be used to increase diabetes-related knowledge and self-care behaviours and to improve glycemic control [Grade A, Level 1A (46,47,50)].

10. Adding literacy- and numeracy-sensitive materials to comprehensive diabetes management education and support programs may improve knowledge, self-efficacy and A1C outcomes for people with low literacy [Grade C, Level 3 (52)].

Abbreviations:
AIC, glycated hemoglobin; *SME*, self-management education; *SMS*, self-management support.

Other Relevant Guidelines

Organization of Diabetes Care, p. S27
Monitoring Glycemic Control, p. S47
Diabetes and Mental Health, p. S130
Type 1 Diabetes in Children and Adolescents, p. S234

Author Disclosures

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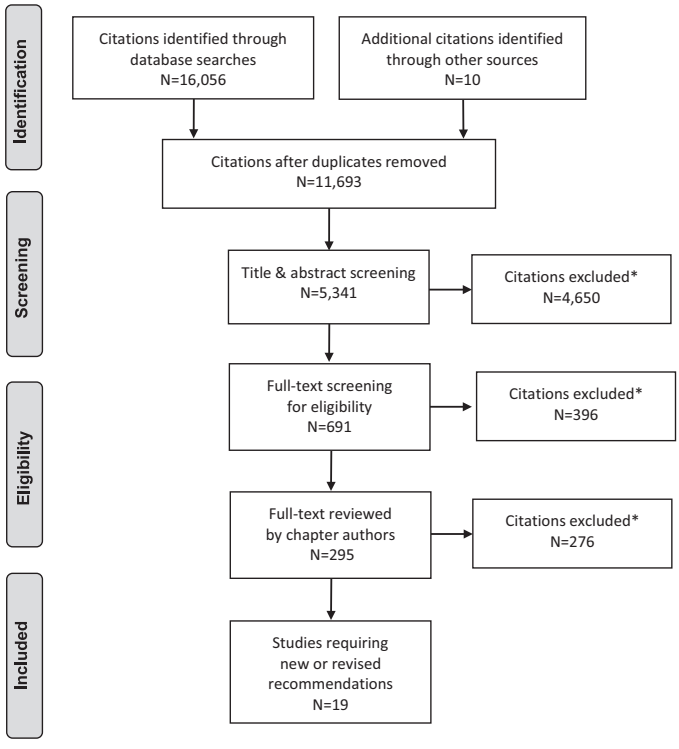
Literature Review Flow Diagram for Chapter 7: Self-Management Education and Support



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (90).

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2018 Clinical Practice Guidelines

Targets for Glycemic Control

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Optimal glycemic control is fundamental to the management of diabetes.
- Both fasting and postprandial plasma glucose levels correlate with the risk of complications and contribute to the measured glycated hemoglobin (A1C) value.
- Glycemic targets should be individualized based on the individual's frailty or functional dependence and life expectancy.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Try to keep your blood glucose as close to your target range as possible. This will help to delay or prevent complications of diabetes.
- Target ranges for blood glucose and A1C can vary and depend on a person's medical conditions and other risk factors. Work with your diabetes health-care team to determine your target A1C and blood glucose target range (fasting and after meals).

Introduction

Optimal glycemic control is fundamental to the management of diabetes. Regardless of the underlying treatment, glycated hemoglobin (A1C) levels >7.0% are associated with a significantly increased risk of both microvascular and cardiovascular (CV) complications (1–3). The initial data from the Diabetes Control and Complications Trial (DCCT; type 1 diabetes) (2) and the United Kingdom Prospective Diabetes Study (UKPDS; type 2 diabetes) (3) demonstrated a curvilinear relationship between A1C and diabetes complications, with no apparent threshold of benefit, although the absolute reduction in risk was substantially less at lower A1C levels. Similarly, both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) are directly correlated to the risk of complications, with some evidence that PPG might constitute a stronger independent risk factor for CV complications (4–10).

Evidence indicates that improved glycemic control reduces the risk of both microvascular and CV complications. The initial prospective randomized controlled trials were conducted in people with recently diagnosed diabetes. These trials—the DCCT in type 1 diabetes (11), the Kumamoto trial (12) and the UKPDS (1,13) in type 2 diabetes—confirmed that improved glycemic control significantly reduced the risk of microvascular complications, but had no significant effect on CV outcomes. Subsequent observational data from long-term follow up after termination of randomization periods of both the DCCT and UKPDS cohorts showed a persistence of significant microvascular benefits and also demonstrated an emergence of beneficial effect on CV outcomes attributed to intensive glycemic control. This has been termed as "metabolic memory" or "legacy effect" (14–16). In the DCCT cohort, there was a significant reduction in CV outcomes (42%), nonfatal myocardial infarct (MI), stroke and CV death (57%), as well as all-cause mortality (33%) in previously intensively treated participants compared with those who were previously in the standard arm (17–19). Similarly, there was a significant reduction in MI (15% to 33%) and all-cause mortality (13% to 27%) in the UKPDS cohort in participants who had been originally randomized to intensive treatment (16).

Whereas the UKPDS trial enrolled people with recently diagnosed type 2 diabetes, 3 major subsequent trials—the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT)—examined the effect of intensive glycemic control on people with long-standing type 2 diabetes. The ACCORD trial randomly assigned 10,251 participants who had either a previous history of cardiovascular disease (CVD) or multiple risk factors for CVD, and a baseline A1C level ≥7.5% to intensive therapy targeting an A1C <6.0% or standard therapy targeting an A1C level of 7.0% to 7.9% (20,21). The mean age of participants was 62 years and the mean duration of diabetes was 10 years. A difference in A1C was rapidly obtained and maintained throughout the trial at 6.4% and 7.5% in the intensive and standard therapy groups, respectively. The primary composite major CV outcomes (nonfatal MI, nonfatal stroke or death from CV causes) were not reduced significantly in ACCORD (hazard ratio [HR] 0.90, p=0.16). The glycemic control portion of the trial was prematurely terminated after 3.5 years due to higher mortality (1.41% vs. 1.14% per year, HR 1.22) associated with assignment to the intensive-treatment arm (19,20). However, an observational follow up of the surviving ACCORD participants over a median of 8.8 years showed a neutral long-term effect of intensive glucose control on the composite outcome and all-cause mortality (HR 1.01, confidence interval [CI] 0.92–1.10) (22).

Conflict of interest statements can be found on page S44.

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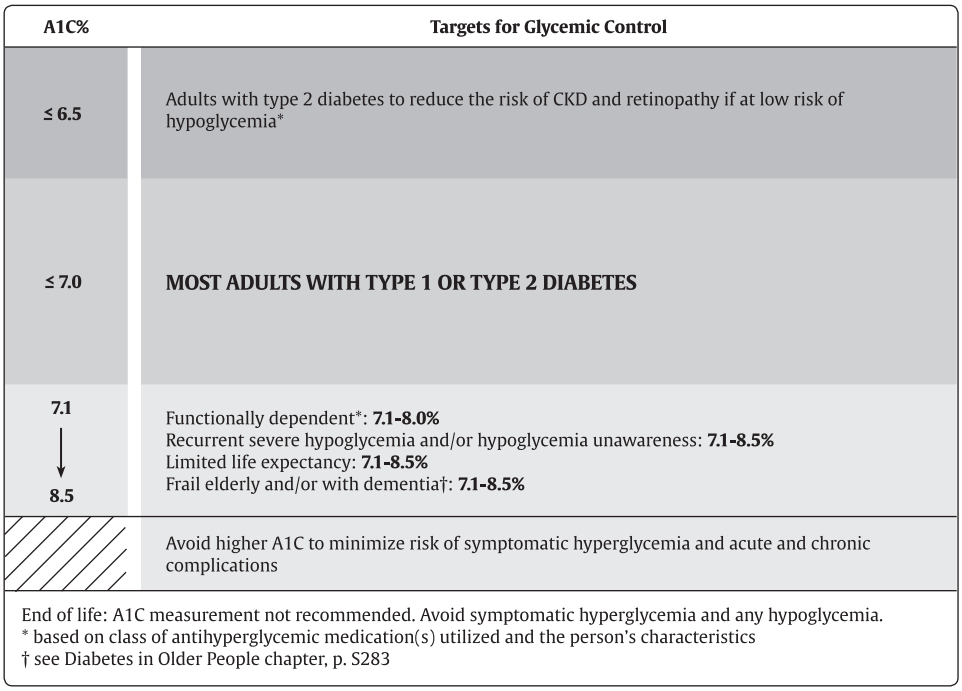

Figure 1. Recommended targets for glycemic control.
A1C, glycated hemoglobin; *CKD*, chronic kidney disease.

The ADVANCE trial randomly assigned 11,140 participants to standard (targeting A1C based on local guidelines) or intensive glucose control therapy aimed at reducing A1C ≤6.5% (23). Participants were ≥55 years of age with a history of major CV or microvascular disease or at least 1 other risk factor for CVD. The mean duration of diabetes was 8 years. After a 5-year follow up, mean A1C was 6.5% in the intensive group and 7.3% in the standard group. The primary outcome was a composite of microvascular events (nephropathy and retinopathy) and CV disease defined by major adverse CV events. There was significant reduction in the incidence of major microvascular events in the intensive control group, mainly through a 21% relative reduction in nephropathy (23); however, no beneficial effect of intensive glucose lowering was found on major CV events or all-cause mortality either during the trial or the subsequent median observational follow up of 5.4 years (24).

The VADT randomly assigned 1,791 United States military veterans with a mean duration of diabetes being 12 years and with poor glycemic control (≥7.5%) to either standard or intensive glucose therapy, which aimed for an overall reduction in A1C levels by 1.5% (25,26). The mean duration of diabetes was 12 years and the A1C levels achieved in the standard and intensive therapy groups were 8.4% and 6.9%, respectively. During a median follow up of 5.6 years, there was a nonsignificant reduction in the primary outcome (first occurrence of a major CV event), but the progression to albuminuria was significantly reduced in the intensive-treatment participants, with 9.1% of participants having significantly reduced progression compared to 13.8% in the standard therapy group. However, during an observational median follow up of 9.8 years, the intensive-therapy group had a significantly lower risk of the primary outcome (MI, stroke, new or worsening congestive heart failure [CHF], amputation for ischemic gangrene, or CV-related death) than did the standard therapy group (HR 0.83, p=0.04), with an absolute reduction in risk of 8.6 major CV events per 1,000 person-years (27).

Data from a meta-analysis suggest that people with type 2 diabetes who receive intensive glucose lowering therapy have a reduced risk of the composite major adverse CV events (MACE) and MI, with no significant effect on the risk of total mortality, cardiac death, stroke and CHF (28). Although an explanation for the unexpected higher mortality rates associated with intensive-treatment in the ACCORD study remains elusive (29), the frequency of severe hypoglycemia in these trials was 2 to 3 times higher in the intensive therapy groups and a higher mortality was reported in participants with 1 or more episodes of severe hypoglycemia in the ACCORD (30), ADVANCE (31) and VADT trials (25), irrespective of the different treatment arms in which individual participants were allocated. Therefore, it has been suggested that a tight glycemic control with a target A1C of 6.0% may not be ideal for older/frail individuals, those with longer duration of diabetes, advanced coronary artery disease (CAD) and a known history of severe hypoglycemia (32,33) (see Diabetes in Older People chapter, p. S283; Hypoglycemia chapter, p. S104). Higher glycemic targets are also appropriate for functionally dependent adults of any age or individuals with limited life expectancy and little likelihood of benefit from intensive therapy.

Evidence also supports the use of multifactorial risk-reduction strategies in addition to A1C control for CV prevention, including blood pressure (BP) and lipid targets; CV prevention medications; physical activity and other healthy behaviours; as well as smoking cessation (see Cardiovascular Protection in People with Diabetes chapter, p. S162). Such multifactorial interventions have recently been suggested to lead to not only significant microvascular and CV benefits but also mortality reduction in the 21-year follow up of the Steno-2 study (34). The salient results of this study include: increased survival for a median of 7.9 years; 8.1 years longer median time before first CV event; and reduction in all microvascular complications, except for peripheral neuropathy, for participants in the intensive-therapy group compared to the conventional therapy group.

A1C measurement encompasses a component of both the FPG and postprandial PG. In addition, mean glucose values also correlate with A1C in both type 1 and type 2 diabetes as shown in Figure 1 (35,36). When A1C values are higher, the major contribution is the FPG levels, but as the A1C value approaches the target value of ≤7.0%, there is a greater contribution from PPG values (37–39). Another

Table 1
Correlation between A1C and estimated mean glucose values

A1C values (%)	5.5–6.5	6.5–6.9	7.0–7.4	7.5–7.9	8.0–8.5
Estimated mean glucose (mmol/L)	6.2–7.7	7.8–8.5	8.6–9.3	9.4–10.1	10.2–10.9

A1C, glycated hemoglobin.

study using continuous glucose monitoring (CGM) demonstrated that a 2-hour PPG <8.0 mmol/L correlates best with an A1C <7.0% (40). In 1 study of forced intensified antihyperglycemic treatment in 164 participants with type 2 diabetes with A1C not at target (≥7.5%), achievement of a target A1C <7.0% was associated with a FPG target of <5.5 mmol/L in 64% of participants, and a PPG target of <7.8 mmol/L in 94% of participants (38). In addition, several insulin treat-to-target trials have safely used dose titration protocols in individuals not at target A1C to reach lower than "traditional" FPG and PPG targets, including: FPG levels of 4.5 to 5.5 mmol/L in participants with type 2 diabetes (41,42); FPG levels of 4.0 to 5.5 mmol/L in participants with type 2 diabetes (43–46); FPG levels of 3.9 to 5.0 mmol/L in participants with type 1 diabetes (47), as well as protocols targeting both FPG levels of 4.5 to 5.5 mmol/L and 2-hour PG levels of 5.0 to 7.0 mmol/L in participants with type 2 diabetes (48).

However, a major challenge in attempting to use evidence-based observations to determine the value of tighter PPG control has been the lack of well-designed, long-term outcome studies where assessing PPG values is the major objective of the study. Most of the large outcome trials conducted so far have been mostly based on preprandial glucose and A1C targets, with limited evidence of a long-term benefit of targeting PPG alone (49,50).

Although, nontraditional glycemic targets, such as fructosamine and glycated albumin, have also been associated with CV outcomes and mortality in a cohort study (51), the broader utility of such targets and their correlation with A1C has not yet been established.

Finally, glucose variability (GV) as an additional therapeutic goal has recently been gaining support. Limited data support the possibility that GV is involved in the pathogenesis of vascular complications of diabetes by inducing inflammatory activation and oxidative stress (52,53). Key components of GV (variability in FPG and PPG, as well as hypoglycemia) have received some prominence in clinical literature recently, linking these components to diabetes complications. In a cohort of >5,000 people with type 2 diabetes, time-dependent variation of fasting glycemia was a strong predictor of all-cause and CV mortality (53). Specific clinical targets suggested in the literature for people monitored via CGM include minimizing daily glucose standard deviation (SD) (to less than 3 times the mean BG), maximizing time in range (3.9 to 10 mmol/L) and minimizing hypoglycemia duration, severity and frequency. However, management strategies that would minimize glucose variability and their impact on hard clinical outcomes remain to be determined before these novel measurement targets of glucose quality can systematically be incorporated into clinical practice guidelines.

Conclusions

Intensive glucose control with lowering A1C values to ≤7.0% in both type 1 and type 2 diabetes provides strong benefits for microvascular complications and, if achieved early in the disease with avoidance of hypoglycemia and glucose variability as part of a multifactorial treatment approach, likely provide a significant CV benefit. More intensive glucose control, A1C ≤6.5%, may be sought in people with a shorter duration of diabetes and longer life expectancy, especially in those people who are on treatment with antihyperglycemic agents with a low risk of hypoglycemia. An A1C target ≤8.5% may be more appropriate in people with type 1 and type 2 diabetes with limited life expectancy, higher level of functional dependency and a history of repeated severe hypoglycemia with hypoglycemia unawareness.

RECOMMENDATIONS

1. Glycemic targets should be individualized [Grade D, Consensus].
2. In most people with type 1 or type 2 diabetes, an A1C ≤7.0% should be targeted to reduce the risk of microvascular [Grade A, Level 1A (1,2,22,23)] and, if implemented early in the course of disease, CV complications [Grade B, Level 3 (23)].
3. In people with type 2 diabetes, an A1C ≤6.5% may be targeted to reduce the risk of CKD [Grade A, Level 1A (23)] and retinopathy [Grade A, Level 1A (21)], if they are assessed to be at low risk of hypoglycemia based on class of antihyperglycemic medication(s) utilized and the person's characteristics [Grade D, Consensus].
4. A higher A1C target may be considered in people with diabetes with the goals of avoiding hypoglycemia and over-treatment related to antihyperglycemic therapy, with any of the following [Grade D, Consensus for all]:
   a. Functionally dependent: 7.1%–8.0%
   b. History of recurrent severe hypoglycemia, especially if accompanied by hypoglycemia unawareness: 7.1%–8.5%
   c. Limited life expectancy: 7.1%–8.5%
   d. Frail elderly and/or with dementia: 7.1%–8.5%
   e. End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia.
5. In order to achieve an A1C ≤7.0%, people with diabetes should aim for:
   a. FPG or preprandial PG target of 4.0 to 7.0 mmol/L and a 2-hour PPG target of 5.0–10.0 mmol/L [Grade B, Level 2 (2) for type 1; Grade B, Level 2 (1) for type 2 diabetes]
   b. If an A1C target ≤7.0% cannot be achieved with a FPG target of 4.0–7.0 mmol/L and PPG target of 5.0–10.0 mmol/L, further FPG lowering to 4.0 to 5.5 mmol/L and/or PPG lowering to 5.0–8.0 mmol/L may be considered, but must be balanced against the risk of hypoglycemia [Grade D, Level 4 (38) for FPG target for type 2 diabetes; Grade D, Consensus for FPG target for type 1 diabetes; Grade D, Level 4 (38,40) for PPG target for type 2 diabetes; Grade D, Consensus for PPG target for type 1 diabetes].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *CGM*, continuous glucose monitoring; *CHF*, congestive heart failure, *CI*, confidence interval; *CKD*, chronic kidney disease; *CV*; cardiovascular; *FPG*, fasting plasma glucose; *GV*, glucose variability *HR*, hazard ratio; *MI*, myocardial infarct; *PG*, plasma glucose; *PPG,* postprandial plasma glucose.

Author Disclosures

Dr. Bajaj reports personal fees from Abbott; grants and personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi, outside the submitted work. Dr. Ross reports personal fees from Novo Nordisk, Eli Lilly, Janssen, AstraZeneca, and Boehringer Ingelheim, outside the submitted work. No other authors have anything to disclose.

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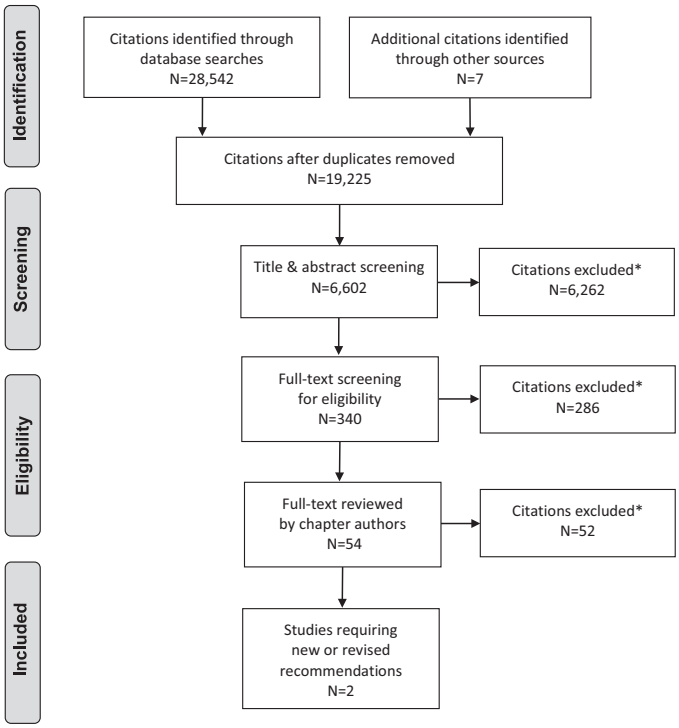
Literature Review Flow Diagram for Chapter 8: Targets for Glycemic Control



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (54).

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2018 Clinical Practice Guidelines

Monitoring Glycemic Control

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Glycated hemoglobin (A1C) is a valuable indicator of glycemic treatment effectiveness and should be measured at least every 3 months when glycemic targets are not being met and when antihyperglycemic therapy is being adjusted. In some circumstances, such as when significant changes are made to therapy or during pregnancy, it is appropriate to check A1C more frequently.
- Awareness of all measures of glycemia—self-monitored blood glucose results, including self-monitored blood glucose (SMBG), flash glucose monitoring (FGM), continous glucose monitoring (CGM) and A1C—provides the best information to assess glycemic control.
- Self-monitoring of blood glucose, FGM and CGM should not be viewed as glucose-lowering interventions, but rather as aids to assess the effectiveness of glucose-lowering interventions and to prevent and detect hypoglycemia.
- Timing and frequency of SMBG may be determined individually based on the type of diabetes, the type of antihyperglycemic treatment prescribed, the need for information about blood glucose levels and the individual's capacity to use the information from testing to modify healthy behaviours or self-adjust antihyperglycemic agents.
- SMBG, FGM and CGM linked with a structured educational and therapeutic program designed to facilitate behaviour change can improve blood glucose levels and prevent hypoglycemia.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- A1C is a measurement of your average blood glucose control for the last 2 to 3 months. Approximately 50% of the value comes from the last 30 days.
- You should have your A1C measured every 3 months when your blood glucose targets are not being met or when you are making changes to your diabetes management. In some circumstances, such as when significant changes are made to your glucose-lowering therapy or during pregnancy, your health-care provider may check your A1C more frequently.
- Checking your blood glucose with a glucose meter (also known as self-monitoring of blood glucose) or using a flash glucose meter or continuous glucose monitor will:
  - Determine if you have a high or low blood glucose at a given time
  - Show how your health behaviours and diabetes medication(s) affect your blood glucose levels
  - Help you and your diabetes health-care team to make health behaviour and medication changes that will improve your blood glucose levels.
- Discuss with your diabetes health-care team how often you should check your blood glucose level.

A1C Testing

Glycated hemoglobin (A1C) is a reliable estimate of mean plasma glucose (PG) levels over the previous 8 to 12 weeks (1). The mean blood glucose (BG) level in the 30 days immediately preceding the blood sampling (days 0 to 30) contributes 50% of the result and the prior 90 to 120 days contributes 10% (2,3). In uncommon circumstances, where the rate of red blood cell turnover is significantly shortened or extended, or the structure of hemoglobin is altered, A1C may not accurately reflect glycemic status (Table 1).

A1C is the preferred standard for assessing glycated hemoglobin, and laboratories are encouraged to use assay methods that are standardized to the Diabetes Control and Complications Trial (DCCT) reference (4–6). A1C is a valuable indicator of treatment effectiveness and should be measured at least every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted or changed. Testing at 6-month intervals may be considered in situations where glycemic targets are consistently achieved (4,7). In some circumstances, such as when significant changes are made to therapy, or during pregnancy, it is appropriate to check A1C more frequently (see Diabetes and Pregnancy chapter, p. S255).

A1C may also be used for the diagnosis of diabetes in adults (see Screening for Diabetes in Adults chapter, p. S16). In Canada, A1C is reported using the National Glycohemoglobin Standardization Program (NGSP) units (%). In 2007, a consensus statement from the American Diabetes Association, European Association for the Study of Diabetes and the International Diabetes Federation called for A1C reporting worldwide to change to dual reporting of A1C with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) SI units (mmol/mol) and derived NGSP units (%) with the hope of fully converting to exclusive reporting in SI units (8). However, this has not been adopted worldwide, and both Canada and the United States still use the NGSP units (%) (9). Although there are some advantages to reporting in SI units, the most notable disadvantage is the massive education effort that would be required to ensure recognition and adoption of the new units. Canada is currently not performing dual reporting; therefore, throughout this document, A1C is still written in NGSP units (%). For those who wish to convert NGSP units to SI units, the following equation can be used: IFCC = 10.93 (NGSP) – 23.50 (10) (see Appendix 15. Glycated Hemoglobin Conversion Chart for conversion of A1C from NGSP units to IFCC SI units).

Point-of-care A1C analyzers are bench-top instruments that use a finger-prick capillary blood sample. They are designed for use in a health-care provider's office, a treatment room or at a bedside. The blood is applied to a test cartridge and the sample is analyzed

Conflict of interest statements can be found on page S51.

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Table 1
Factors that can affect A1C

Factor	Increased A1C	Decreased A1C	Variable change in A1C
Erythropoiesis	Iron deficiency B12 deficiency Decreased erythropoiesis	Use of erythropoietin, iron or B12 Reticulocytosis Chronic liver disease	
Altered hemoglobin			Fetal hemoglobin Hemoglobinopathies Methemoglobin Genetic determinants
Altered glycation	Alcoholism Chronic renal failure Decreased erythrocyte pH	Ingestion of aspirin, vitamin C or vitamin E Hemoglobinopathies Increased erythrocyte pH	
Erythrocyte destruction	Increased erythrocyte lifespan: Splenectomy	Decreased erythrocyte lifespan: Chronic renal failure Hemoglobinopathies Splenomegaly Rheumatoid arthritis Antiretrovirals Ribavirin Dapsone	
Assays	Hyperbilirubinemia Carbamylated hemoglobin Alcoholism Large doses of aspirin Chronic opiate use	Hypertriglyceridemia	Hemoglobinopathies

A1C, glycated hemoglobin.

within several minutes (11). Point-of-care A1C testing has several potential advantages over laboratory A1C testing, including rapid test results to expedite medical decision-making, convenience for people with diabetes, potential improved health system efficiency and improved access to testing for underserved populations (12). A number of point-of-care A1C devices are commercially available for monitoring glycemic control; however, a United Kingdom systematic review concluded that evidence of the impact of using point-of-care A1C testing on medication use, clinical decision-making and participants' outcomes is lacking, and that a randomized trial with economic evaluation is needed (13). Currently, no point-of-care A1C analyzers are approved for the diagnosis of diabetes.

Several studies have shown that A1C concentrations are higher in some ethnic groups (African, Asian, Hispanic) than in Caucasian persons with similar plasma glucose concentrations (14–19). In 1 cross-sectional study, A1C was 0.13 to 0.47 percentage points higher in African American than in Caucasian persons, with the difference increasing as glucose intolerance worsened. However, all of these studies estimated mean glucose levels on the basis of very limited measurements and, as a result, it is not clear whether the higher A1C observed in certain ethnic groups is due to worse glycemic control or racial variation in the glycation of hemoglobin. If differences in A1C between ethnic groups exist, the differences appear to be small and have not been shown to significantly modify the association between A1C and cardiovascular outcomes (20), retinopathy (21) or nephropathy (22).

Self-Monitoring of Blood Glucose

Monitoring blood glucose levels, whether using traditional self monitoring of blood glucose (SMBG) devices or more recent flash glucose monitoring (FGM), can serve as a useful adjunct to other measures of glycemia, including A1C. Most people with diabetes benefit from monitoring BG for a variety of reasons (23,24). Monitoring BG is the optimal way to confirm and appropriately treat hypoglycemia. It can provide feedback on the results of healthy behaviour interventions and antihyperglycemic pharmacological treatments. It can increase one's empowerment and adherence to treatment. It can also provide information to both the person with diabetes and their diabetes health-care team to facilitate longer-term treatment modifications and titrations as well as shorter-term treatment decisions, such as insulin dosing for people with type 1 or type 2 diabetes. Finally, in situations where A1C does not accurately reflect glycemia (Table 1), monitoring BG is necessary to adequately monitor glycemia (25).

Monitoring BG is most effective when combined with an education program that incorporates instruction for people with diabetes on healthy behaviour changes in response to BG values and for health-care providers on how to adjust antihyperglycemic medications in response to BG readings (26–30). As part of this education, people with diabetes should receive instruction on how and when to perform self-monitoring; how to record the results in an organized fashion; the meaning of various BG levels and how behaviour and actions affect BG results.

Frequency of SMBG

The recommended frequency of monitoring BG may be individualized to each person's unique circumstances. Factors influencing this recommendation include type of diabetes, type of antihyperglycemic therapy, changes to antihyperglycemic therapy, adequacy of glycemic control, literacy and numeracy skills, propensity to hypoglycemia, awareness of hypoglycemia, occupational requirements and acute illness.

Type 1 and type 2 diabetes treated with insulin. For people with type 1 diabetes, monitoring BG is essential to achieving and maintaining good glycemic control. In a large cohort study, performance of ≥3 self-tests per day was associated with a statistically and clinically significant 1.0% absolute reduction in A1C (8). The evidence is less certain in people with type 2 diabetes treated with insulin, although the above principle likely applies (8). In a large, non-randomized study of individuals with stable type 2 diabetes using insulin, testing at least 3 times a day was associated with improved glycemic control (31). More frequent testing, including preprandial and 2-hour postprandial PG (31,32) and occasional overnight BG measurements,

is often required to provide the information needed to reduce hypoglycemia risk, including unrecognized nocturnal hypoglycemia (33–37).

Type 2 diabetes not treated with insulin. For people with type 2 diabetes treated with healthy behaviour interventions, with or without noninsulin antihyperglycemic agents, the effectiveness and frequency of monitoring BG in improving glycemic control is less clear (23,24,38–47). A series of recent meta-analyses, all using different methodologies and inclusion criteria, have generally shown a small benefit to reducing A1C in those individuals performing SMBG compared to those who did not (48–54). The magnitude of the benefit is small, with absolute A1C reductions ranging from 0.2% to 0.5%. These analyses demonstrated greater A1C reductions in those performing SMBG when the baseline A1C was >8% (30,48,51,55). SMBG has been demonstrated to be most effective in persons with type 2 diabetes within the first 6 months after diagnosis (56). Also of significance, there is no evidence that SMBG affects one's satisfaction, general well-being or general health-related quality of life (56).

Most trials in noninsulin-treated people with type 2 diabetes are of limited value as baseline A1C levels were typically <8.0%, and the trials did not include a component of educational and therapeutic intervention in response to BG values. Several recent, well-designed randomized controlled trials that have included this component have demonstrated reductions in A1C (30,57,58). In the Structured Testing Program (STeP) trial, 483 poorly controlled participants with diabetes not on insulin (mean A1C >8.9%) were randomized to either an active control group with enhanced usual care or a structured testing group with enhanced usual care and at least quarterly use of structured SMBG (30). At 1 year, there was a significantly greater reduction in mean A1C in the structured testing group compared with the active control group (–0.3%, p=0.04). Significantly more structured testing group participants received a treatment change recommendation compared with active control group participants. In the Role of Self-Monitoring of Blood Glucose and Intensive Education in Patients with Type 2 Diabetes Not Receiving Insulin (ROSES) trial, participants were randomly allocated to either a self-monitoring-based diabetes management strategy with education on how to modify health behaviours according to SMBG readings or to usual care (57). Results of SMBG were discussed during monthly telephone contact. After 6 months, significantly greater reductions in mean A1C (–0.5%, p=0.04) and body weight (–4.0 kg, p=0.02) were observed in the SMBG group compared with the usual care group. In the St. Carlos trial, newly diagnosed people with type 2 diabetes were randomized to either an SMBG-based intervention or an A1C-based intervention (58). In the SMBG intervention group, SMBG results were used as both an educational tool to promote adherence to healthy behaviour modifications as well as a therapeutic tool for adjustment of antihyperglycemic pharmacologic therapy. Treatment decisions for the A1C cohort were based strictly on A1C test results. After 1 year of follow up, median A1C level and body mass index (BMI) were significantly reduced in participants in the SMBG intervention group (from 6.6% to 6.1%, p<0.05; and from 29.6 kg to 27.9 kg, p<0.01). In the A1C-based intervention group, there was no change in median A1C or BMI. The evidence is less clear about how often, once recommended, SMBG should be performed by persons with type 2 diabetes not treated with insulin.

Separate from the ability of the person with diabetes to use self-monitored glucose to lower A1C, monitoring glucose should be considered for the prevention, recognition and treatment of hypoglycemia in persons whose regimens include an insulin secretagogue due to the higher risk of hypoglycemia with this class of antihyperglycemic agents (59). On the other hand, for people with type 2 diabetes who are managed with healthy behaviour interventions, with or without non-insulin antihyperglycemic agents associated with low risk of hypoglycemia, and who are meeting glycemic targets, very infrequent monitoring may be needed (see Appendix 5. Self-Monitoring of Blood Glucose [SMBG] Recommendation Tool for Health-Care Providers).

Verification of accuracy of SMBG performance and results

Variability can exist between BG results obtained using SMBG devices and laboratory testing of PG. At BG levels >4.2 mmol/L, a difference of <15% between SMBG and simultaneous venous fasting plasma glucose (FPG) (after at least an 8-hour fast), is considered acceptable (60). In order to ensure accuracy of SMBG, results should be compared with a laboratory measurement of FPG at least annually or when A1C does not match SMBG readings. Periodic re-education on correct SMBG technique may improve the accuracy of SMBG results (61,62). In rare situations, therapeutic interventions may interfere with the accuracy of some SMBG devices. For example, icodextrin-containing peritoneal dialysis solutions may cause falsely high readings in meters utilizing glucose dehydrogenase. Care should be taken to select an appropriate meter with an alternative glucose measurement method in such situations.

Alternate site testing

Meters are available that allow SMBG using blood samples from sites other than the fingertip (forearm, palm of the hand, thigh). Accuracy of results over a wide range of BG levels and during periods of rapid change in BG levels is variable across sites. During periods of rapid change in BG levels (e.g. after meals, after exercise and during hypoglycemia), fingertip testing has been shown to more accurately reflect glycemic status than forearm or thigh testing (63,64). In comparison, blood samples taken from the palm near the base of the thumb (thenar area) demonstrate a closer correlation to fingertip samples at all times of day and during periods of rapid change in BG levels (65,66).

Ketone Testing

Ketone testing is recommended for all individuals with type 1 diabetes during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain elevated (>14.0 mmol/L), or when symptoms of diabetic ketoacidosis (DKA) (such as nausea, vomiting or abdominal pain) are present (4). If all of these conditions are present in type 2 diabetes, ketone testing should be considered, as DKA also can occur in these individuals.

During DKA, the equilibrium that is usually present between ketone bodies shifts toward formation of beta-hydroxybutyric acid (beta-OHB). As a result, testing methods that measure blood beta-OHB levels may provide more clinically useful information than those that measure urine acetoacetate or acetone levels. Assays that measure acetoacetate through urine testing may not identify the onset and resolution of ketosis as quickly as those that quantify beta-OHB levels in blood, since acetoacetate or acetone can increase as beta-OHB decreases with effective treatment (60). Meters that quantify beta-OHB from capillary sampling may be preferred for self-monitoring of ketones, as they have been associated with earlier detection of ketosis and may provide information required to prevent progression to DKA (66–68). This may be especially useful for individuals with type 1 diabetes using continuous subcutaneous insulin (CSII) therapy, as interruption of insulin delivery can result in rapid onset of DKA (69).

Continuous Glucose Monitoring Systems

Continuous glucose monitoring (CGM) systems measure glucose concentrations in the interstitial fluid. Two types of devices are

available. The "real time" (also called "personal") CGM provides information directly to the user by displaying moment-to–moment absolute glucose levels and trending arrows, and by providing alarm notifications in the event that the glucose level is above or below a preset limit. A "blinded" (sometimes referred to as "professional") CGM captures, but does not display, the glucose readings, which are then downloaded onto a computer for viewing and retrospective analysis by the health-care provider (typically in conjunction with the user).

CGM technology incorporates a subcutaneously inserted sensor, an attached transmitter and, in the case of real-time CGM, a display unit (which may be a stand-alone unit or be integrated into an insulin pump). In professional CGM, the "transmitter" captures and retains the data. In Canada, 2 real-time CGM and 2 professional CGM are available. Real-time CGM has been consistently shown to reduce A1C in both adults (70–81) and children (71,73,75,76,78,79,82) with type 1 diabetes with and without CSII, and to reduce A1C in adults with type 2 diabetes (83). Real-time CGM also has been shown to reduce the time spent in hypoglycemia (78,80,81,84). Professional CGM has been shown to reduce A1C in adults with type 2 diabetes (85) and in pregnant women with type 1 or type 2 diabetes (86).

Successful use of CGM is dependent on adherence with duration of time the CGM is used. The greater the time wearing the device, typically the better the A1C (72,73,76,77,82,86). Like SMBG, CGM provides the best outcomes if it is associated with structured educational and therapeutic programs. CGM is not a replacement for SMBG because SMBG is still required for calibration of the CGM device. Some real-time CGM devices require SMBG to confirm interstitial measurements prior to making therapeutic changes or treating suspected hypoglycemia; whereas other devices only require SMBG if glucose alerts and readings do not match symptoms.

Flash Glucose Monitoring

Flash glucose monitoring (FGM) also measures glucose concentration in the interstitial fluid, however, FGM differs from CGM technology in several ways. FGM is factory calibrated and does not require capillary blood glucose (with SMBG device) calibration. BG levels are not continually displayed on a monitoring device but instead are displayed when the sensor is "flashed" with a reader device on demand. The FGM reader also displays a plot profile of the last 8 hours, derived from interpolating glucose concentrations recorded every 15 minutes. Therefore, when the person with diabetes performs ≥3 sensor scans per day at ≤8 hour intervals, the FGM records 24-hour glucose profiles. The sensor can be worn continuously for up to 14 days. The device does not provide low or high glucose alarms.

In the Randomised Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on Hypoglycaemia in Type 1 Diabetes (IMPACT) trial, FGM without the use of SMBG decreased hypoglycemia in participants with well-controlled type 1 diabetes (A1C <7.5%) on either MDI or CSII, an average of 74 minutes per day, for a 38% reduction compared with a control group (87). In addition, a 40% reduction in the time spent in hypoglycemia at night, a 50% reduction in serious hypoglycemia and a reduction of routine SMBG measurements by 91%. In the Randomised Controlled Study to Evaluate the Impact of Novel Glucose Sensing Technology on HbA1c in Type 2 Diabetes trial, in individuals with type 2 diabetes, the use of FGM vs. SMBG resulted in a similar drop in A1C, but a significant reduction in time spent in hypoglycemia, <3.9 mmol/l by 43%, <3.1 mmol/L by 53%, reduced nocturnal hypoglycemia by 54%, reduced glycemic variability and improved quality of life. There was a statistical reduction in A1C for participants <65 years at 3 and 6 months (–0.53% and -0.20% respectively) (88).

RECOMMENDATIONS

1. For most individuals with diabetes, A1C should be measured approximately every 3 months to ensure that glycemic goals are being met or maintained [Grade D, Consensus]. In some circumstances, such as when significant changes are made to therapy, or during pregnancy, it is appropriate to check A1C more frequently. Testing at least every 6 months should be performed in adults during periods of treatment and healthy behaviour stability when glycemic targets have been consistently achieved [Grade D, Consensus].

2. For individuals using insulin more than once a day, SMBG should be used as an essential part of diabetes self-management [Grade A, Level 1 (34), for type 1 diabetes; Grade C, Level 3 (23), for type 2 diabetes] and should be undertaken at least 3 times per day [Grade C, Level 3 (23,31)] and include both pre- and postprandial measurements [Grade C, Level 3 (31,32,89)]. For individuals with type 2 diabetes on once-daily insulin in addition to noninsulin antihyperglycemic agents, testing at least once a day at variable times is recommended [Grade D, Consensus].

3. For individuals with type 2 diabetes not receiving insulin therapy, frequency of SMBG recommendations should be individualized depending on type of antihyperglycemic agents, level of glycemic control and risk of hypoglycemia [Grade D, Consensus].
   a. When glycemic control is not being achieved, SMBG should be instituted [Grade B, Level 2 (46,51)] and should include periodic pre- and postprandial measurements and training of health-care providers and people with diabetes on methods to modify health behaviours and antihyperglycemic medications in response to SMBG values [Grade B, Level 2 (30,90)]
   b. If achieving glycemic targets or receiving antihyperglycemic medications not associated with hypoglycemia, infrequent SMBG is appropriate [Grade D, Consensus].

4. In many situations, for all individuals with diabetes, more frequent SMBG testing should be undertaken to provide information needed to make health behaviour or antihyperglycemic medication adjustments required to achieve desired glycemic targets and avoid risk of hypoglycemia [Grade D, Consensus].

5. In people with type 1 diabetes who have not achieved their glycemic target, real-time CGM may be offered to improve glycemic control [Grade A, Level 1A (71,80,81) for non-CSII users; Grade B, Level 2 for CSII users (71)] and reduce duration of hypoglycemia [Grade A, Level 1A (78,80,84)] in individuals who are willing and able to use these devices on a nearly daily basis.

6. FGM may be offered to people with diabetes to decrease time spent in hypoglycemia [Grade B, Level 2 (87) for type 1 diabetes; Grade B, Level 2 (88) for type 2 diabetes].

7. In order to ensure accuracy of BG meter readings, meter results should be compared with laboratory measurement of simultaneous venous FPG (8-hour fast) at least annually and when A1C does not match glucose meter readings [Grade D, Consensus].

8. Individuals with type 1 diabetes should be instructed to perform ketone testing during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain >14.0 mmol/L or in the presence of symptoms of DKA [Grade D, Consensus]. Blood ketone testing methods may be preferred over urine ketone testing, as they have been associated with earlier detection of ketosis and response to treatment [Grade B, Level 2 (67)].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *BMI*, body mass index *CBG*; capillary blood glucose; *CGM*, continuous glucose monitoring; *CGMS*, continuous glucose monitoring system; *CSII*, continuous subcutaneous infusion infusion; *DKA*, diabetic ketoacidosis; *FGM*; flash glucose monitoring; *FPG*, fasting plasma glucose; *PG*, plasma glucose; *SMBG*, self-monitoring of blood glucose.

Other Relevant Guidelines

Self-Management Education and Support, p. S36
Targets for Glycemic Control, p. S42
Glycemic Management in Adults with Type 1 Diabetes, p. S80
Hypoglycemia, p. S104
Type 1 Diabetes in Children and Adolescents, p. S234

Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255

Relevant Appendices

Appendix 5. Self-Monitoring of Blood Glucose (SMBG) Recommendation Tool for Health-Care Providers
Appendix 15. Glycated Hemoglobin Conversion Chart

Author Disclosures

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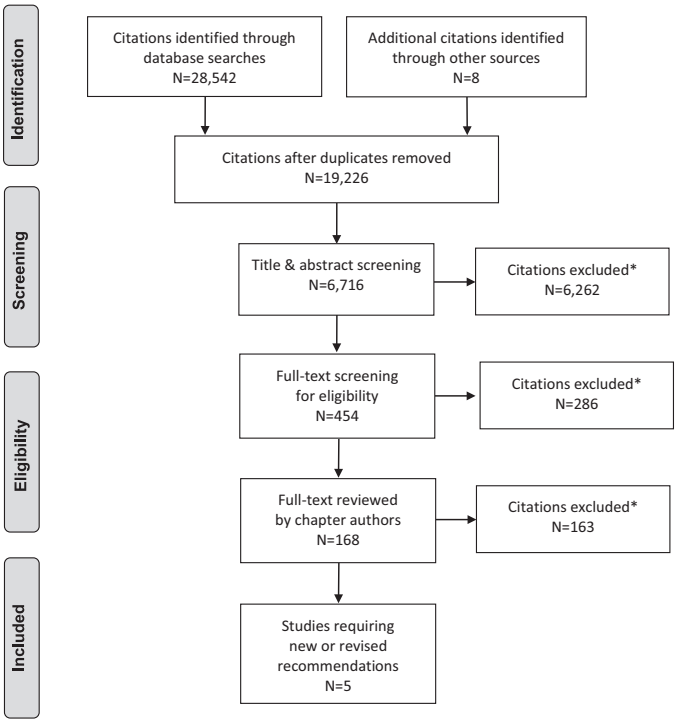
Literature Review Flow Diagram for Chapter 9: Monitoring Glycemic Control



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (91).

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2018 Clinical Practice Guidelines

Physical Activity and Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantially lower morbidity and mortality in people with diabetes.
- Both aerobic and resistance exercise are beneficial, and it is optimal to do both types of exercise. At least 150 minutes per week of aerobic exercise and at least 2 sessions per week of resistance exercise are recommended, though smaller amounts of activity still provide some health benefits.
- A number of strategies that increase self-efficacy and motivation can be employed to increase physical activity uptake and maintenance, such as setting specific physical activity goals, using self-monitoring tools (pedometers or accelerometers) and developing strategies to overcome anticipated barriers.
- For people with type 2 diabetes, supervised exercise programs have been particularly effective in improving glycemic control, reducing the need for noninsulin antihyperglycemic agents and insulin, and producing modest but sustained weight loss.
- Habitual, prolonged sitting is associated with increased risk of death and major cardiovascular events.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Physical activity often improves glucose control and facilitates weight loss, but has multiple other health benefits even if weight and glucose control do not change.
- It is best to avoid prolonged sitting. Try to interrupt sitting time by getting up briefly every 20 to 30 minutes.
- Try to get at least 150 minutes per week of aerobic exercise (like walking, bicycling or jogging).
- Using a step monitor (pedometer or accelerometer) can be helpful in tracking your activity.
- In addition to aerobic exercise, try to do at least 2 sessions per week of strength training (like exercises with weights or weight machines).
- If you decide to begin strength training, you should ideally get some instruction from a qualified exercise specialist.
- If you cannot reach these recommended levels of activity, doing smaller amounts of activity still has some health benefits.

Types of Exercise

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure (1). Exercise is planned, structured physical activity (1) (see Table 1 for definitions of key exercise terms used in this article.) **Aerobic exercise** (like walking, bicycling, swimming or jogging) involves continuous, rhythmic movements of large muscle groups, normally at least 10 minutes at a time. In this chapter, we will refer to this type of exercise as "aerobic" for simplicity, even though when performed at a very high intensity, such as with high-intensity interval training, it also involves some anaerobic metabolism. **Resistance exercise** involves brief repetitive exercises with weights, weight machines, resistance bands or one's own body weight (e.g. push-ups) to increase muscle strength and/or endurance. **Flexibility exercise** (like lower back or hamstring stretching) aims to enhance the ability to move through fuller ranges of motion. Some types of exercise, such as yoga, can incorporate elements of both resistance and flexibility exercise.

Benefits of Physical Activity

Physical activity can help people with diabetes achieve a variety of goals, including increased cardiorespiratory fitness, increased vigour, improved glycemic control, decreased insulin resistance, improved lipid profile, blood pressure (BP) reduction and maintenance of weight loss (2–5).

Randomized trials have found that supervised exercise interventions improve glycated hemoglobin (A1C) (6–8), triglycerides (TG) and cholesterol (9) in people with type 2 diabetes when compared to no exercise comparison groups (10). Cohort studies have demonstrated that, in people with type 2 (11–13), and with type 1 diabetes (14,15), regular physical activity (11–13) and/or moderate to high cardiorespiratory fitness (16) are associated with reductions in cardiovascular (CV) and overall mortality.

Randomized trials have also demonstrated that aerobic exercise training increases cardiorespiratory fitness in both type 1 and type 2 diabetes (17), and slows the development of peripheral neuropathy (18). A meta-analysis (6) found that supervised exercise interventions improved A1C in people with type 2 diabetes when compared to no exercise comparison groups. In addition, interventions involving exercise durations of more than 150 minutes per week were associated with greater A1C reductions (mean change –0.89%) than interventions involving 150 minutes or less of exercise per week (mean change –0.36%) (6). A meta-analysis of head-to-head trials comparing the effects on A1C of aerobic exercise at higher vs. lower intensity found that the interventions with higher intensity reduced A1C more than those of lower intensity (mean A1C difference –0.22%) (8). It was unclear whether the greater

Conflict of interest statements can be found on page S60.

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Table 1
Definitions of terms

Physical activity	Any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels. This term broadly encompasses exercise, sport and physical activities done as a part of daily living, occupation, leisure and active transport.
Exercise	Planned, structured physical activity typically performed with the intent of improving health and/or fitness.
Aerobic exercise	Exercise that involves continuous, rhythmic movements of large muscle groups, such as walking, bicycling, swimming or jogging, normally lasting for at least 10 minutes at a time. This type of exercise depends primarily on the aerobic energy-generating processes in the body (i.e. heart, lungs, cardiovascular system and the oxidation of fuels in skeletal muscle). Moderate-intensity aerobic activities range from 3–6 metabolic equivalents (METS) and include brisk walking, dancing, light cycling, gardening and domestic chores. Vigorous-intensity activities (>6 METS) include running, climbing stairs or hill walking, fast cycling or swimming, aerobics and most competitive sports and games.
Resistance exercise	Brief repetitive exercise using weights, weight machines, resistance bands or one's own body weight (e.g. push-ups) to increase muscle strength and/or endurance.
Flexibility exercise	A form of activity, such as lower back or hamstring stretching, that enhances the ability of joints to move through their full range of motion.
Aerobic training	Exercise training involving periods of predominantly aerobic exercise activities, such as running, cycling or swimming, performed for the purpose of enhancing cardiorespiratory fitness, performance and/or health.
Resistance training	Exercise training, involving brief repetitive exercises with weights, weight machines, resistance bands or one's own body weight (e.g. push-ups) performed for the purpose of increasing muscle mass and strength. This type of exercise uses predominantly anaerobic energy-generating systems in skeletal muscle.
High-intensity interval training	A type of aerobic exercise training based on alternating between short periods of vigorous intensity exertion and periods of rest or lower-intensity exercise; commonly performed using a predominantly aerobic exercise modality, such as running or cycling.
Cardiorespiratory fitness	A health-related component of physical fitness defined as the ability of the circulatory, respiratory and muscular systems to supply oxygen during sustained physical activity. Typically measured via a treadmill or cycle ergometer test and expressed as maximal oxygen uptake (VO_2max) relative to body mass or in metabolic equivalents (METS).
Musculoskeletal fitness	Ability of skeletal and muscular systems to perform work (exercise). Muscular strength and muscular endurance are components of musculoskeletal fitness.
Cardiorespiratory endurance	Ability of the heart, lungs and circulatory system to supply oxygen to working muscles efficiently.
Muscular strength	Maximal force or tension level produced by a muscle or muscle group.
Muscular endurance	Ability of muscle to maintain submaximal force levels for extended periods.
Physical fitness	Ability to perform occupational, recreational and daily activities without undue fatigue. A set of measureable health and skill-related attributes that include cardiorespiratory fitness, muscular strength and endurance, body composition, flexibility, balance, agility, reaction time and power.
Maximum oxygen uptake (VO_2max)	Maximum rate of oxygen utilization during exercise.
METS	The ratio of a person's working (exercising) metabolic rate to the resting metabolic rate. One MET is equivalent to the energy expended while sitting at rest.
Sedentary behaviour	An "activity" that involves little or no movement, with an energy expenditure ranging between 1-1.5 METS. Examples include sitting, watching TV, working on a computer, reclining while awake and driving.

benefits of higher-intensity exercise were limited to studies using high-intensity interval training (see next section on interval training).

In contrast to trials in type 2 diabetes, most clinical trials evaluating exercise interventions in adults with type 1 diabetes have not demonstrated a beneficial effect of exercise on glycemic control (19), but 2 recent meta-analyses found that aerobic training lowered A1C in children and youth with type 1 diabetes by 0.5% and 0.85% respectively (20,21), while also lowering body mass index (BMI), TG and total cholesterol levels. A recent large cross-sectional study of 18,028 adults with type 1 diabetes reported an inverse association between physical activity levels and A1C, diabetic ketoacidosis (DKA), BMI and a number of diabetes-related complications, including dyslipidemia, hypertension, retinopathy and microalbuminuria (22). There are no published trials evaluating the effects of exercise training on quality of life in type 1 diabetes.

Benefits of Interval Training

High-intensity interval training involves alternating between short periods of higher and lower-intensity exercise (see Exercise Prescription Examples). High-intensity interval training leads to greater gains in cardiorespiratory fitness in people with or without diabetes (23,24), and improves glycemic control in some studies of people with type 2 diabetes compared to continuous moderate-intensity exercise (24–26).

In people with type 1 diabetes, high-intensity interval exercise appears to be associated with less risk for hypoglycemia than continuous aerobic exercise, at least during the time of the activity (27,28,29). To date, the risks of high-intensity interval training seem comparable to moderate-intensity continuous exercise in previously screened participants with relatively good glycemic control; however, most studies have been small and underpowered (8). A small trial in women with type 2 diabetes (n=17) found that twice-weekly high-intensity interval training reduced abdominal fat (–8.3%) and visceral fat (–24.2%) significantly, but continuous aerobic exercise did not.

Benefits of Resistance Exercise

Resistance training in adults with type 2 diabetes improves glycemic control (as reflected by reduced A1C), decreases insulin resistance and increases muscular strength (30), lean muscle mass (31) and bone mineral density (32,33), leading to enhanced functional status and prevention of sarcopenia and osteoporosis. The optimal resistance training program has not been clearly established in terms of frequency, intensity, type and volume (34). The greatest impact

on A1C is typically seen in studies that had participants progress to 3 sets (with approximately 8 repetitions per set) of resistance-type exercises at moderate to high intensity (i.e. the maximum weight that can be lifted 8 times while maintaining proper form), 3 times per week (35,36) or more (37,38). However, significant reductions in A1C and body fat have been achieved with twice-weekly resistance exercise in combination with regular aerobic exercise (39–41). The effects of resistance exercise and aerobic exercise on glycemic control are additive (42).

Resistance exercise in most of these studies was carried out using weight machines and/or free weights, and these findings cannot necessarily be generalized to other types of resistance exercise, such as resistance bands or exercises utilizing one's own body weight. For example, a recent meta-analysis found that exercise training with resistance bands in people with type 2 diabetes increased strength but had no significant effect on A1C (43). The benefits of resistance exercise in type 1 diabetes are less clear, but small clinical trials suggest improved body composition and strength, enhanced insulin sensitivity and possibly modest reductions in A1C (44). Compared to aerobic exercise, resistance exercise is associated with less hypoglycemia risk for individuals with type 1 diabetes (45,46).

Benefits of Other Types of Exercise

To date, evidence for the beneficial effects of other types of exercise is not as extensive or as supportive as the evidence for aerobic and resistance exercise. Two systematic reviews found that tai chi had no effect on A1C, compared to either sham exercise or usual care in people with diabetes (47,48). Systematic reviews of yoga as an intervention for type 2 diabetes (49–51) have reported reductions in A1C. However, the quality of the studies was generally low and results were highly heterogeneous, limiting any conclusions that may be drawn (see Complementary and Alternative Medicine for Diabetes chapter, p. S154).

No published study has demonstrated any impact of a pure flexibility program on metabolic control, injury risk or any diabetes-related outcome.

Since osteoarthritis can be a barrier to physical activity (52), water-based physical activities, such as swimming, walking or running in a pool, or aquatic fitness classes have been encouraged for people with such comorbidities (53,54). While few high-quality trials exist, a recent meta-analysis suggests aquatic exercise improves A1C compared to no exercise comparison groups and that the improvements are comparable to those obtained with land-based exercise (55).

Supervised vs. Unsupervised Exercise

A systematic review and meta-analysis found that supervised programs involving aerobic or resistance exercise improved glycemic control in adults with type 2 diabetes, whether or not they included dietary co-intervention (6). The same meta-analysis found that unsupervised exercise improved glycemic control only if there was concomitant dietary intervention. A meta-analysis found that trials evaluating resistance exercise with less supervision showed less beneficial impact on glycemic control, insulin resistance and body composition than studies with greater supervision (30). A 1-year randomized trial compared exercise counselling plus twice-weekly supervised aerobic and resistance exercise vs. exercise counselling alone in people with type 2 diabetes and the metabolic syndrome (39). Although self-reported total physical activity increased substantially in both groups, the group receiving the supervised aerobic and resistance exercise training had significantly better results, including greater reductions in A1C, blood pressure (BP), BMI, waist circumference and estimated 10-year CV risk, and greater increases in aerobic fitness, muscle strength and high-density lipoprotein cholesterol (HDL-C) (39).

The Look-AHEAD Trial

The Look AHEAD (Action for Health in Diabetes) trial was the largest randomized trial to date evaluating the efficacy of a physical activity and dietary control intervention (targeting a ≥7% weight loss), in older adults with type 2 diabetes (56). In this study, at least 175 min/week of unsupervised exercise was targeted as part of the intense lifestyle intervention (ILI), while the control group (Diabetes Support and Education—DSE group) received usual care. Major CV event rates were not significantly different in the 2 groups (56). However, the ILI group achieved significantly greater and more sustained improvements in many important secondary outcomes, including weight loss; improved cardiorespiratory fitness; improved glycemic control, BP and lipids with fewer medications; as well as decreased rate of sleep apnea, severe diabetic chronic kidney disease and retinopathy, depression, sexual dysfunction, urinary incontinence and knee pain; as well as better physical mobility maintenance and quality of life, with lower overall healthcare costs (57).

Minimizing Risk of Exercise-Related Adverse Events

Identifying individuals for whom medical evaluation should be considered prior to initiating an exercise program

For most people with and without diabetes, being sedentary is associated with far greater health risks than exercise would be**.** Most people with diabetes who have no symptoms of coronary ischemia do not require medical clearance before starting a low-to-moderate intensity exercise program. However, middle-aged and older individuals with diabetes who wish to undertake very vigorous or prolonged exercise, such as competitive racing, high-intensity interval training with intervals at maximal effort, or long-distance running should be assessed for conditions that may place them at increased risk for an adverse event. Preproliferative or proliferative retinopathy should be treated and stabilized prior to commencement of vigorous exercise. People with severe peripheral neuropathy should be instructed to inspect their feet daily, especially on days they are physically active, and to wear appropriate footwear. Although previous guidelines stated that persons with severe peripheral neuropathy should avoid weight-bearing activity, more recent studies indicate that individuals with peripheral neuropathy may safely participate in moderate weight-bearing exercise provided they do not have active foot ulcers (58–60). Studies also suggest that people with peripheral neuropathy in the feet, who participate in daily weight-bearing activity, are at decreased risk of foot ulceration compared with those who are less active (59).

A resting ECG should be performed, and an exercise ECG stress test should be considered, for individuals with typical or atypical chest discomfort, unexplained dyspnea, peripheral arterial disease, carotid bruits or history of angina, myocardial infarction (MI), stroke or transient ischemic attacks (see Screening for the Presence of Cardiovascular Disease chapter, p. S170) who wish to undertake exercise more intense than brisk walking, especially if considering very intense, prolonged aerobic exercise.

The value and utility of medical screening procedures prior to exercise, such as resting ECG and exercise stress testing in asymptomatic individuals has been the subject of much debate (61). There is now an increased appreciation that exercise testing is a poor predictor of future cardiovascular disease (CVD) events because such

testing detects flow-limiting coronary lesions while sudden cardiac arrest is usually produced by the rapid progression of a previously non-obstructive lesion (62). Nevertheless, identifying individuals who are symptomatic remains very important. People with diabetes should be screened for signs and symptoms consistent with myocardial ischemia, such as chest pain, severe shortness of breath upon exertion and/or syncope. People who are symptomatic, either before or during exercise, should be referred for ECG stress testing and further cardiac evaluation prior to participating or continuing in an exercise program (see Screening for the Presence of Cardiovascular Disease chapter, p. S170).

Minimizing risk of heat-related illness

Performing physical activity, especially in the heat, places individuals at risk for heat-related injuries. The increase in metabolic heat production augments the rate at which heat must be dissipated to the environment to prevent dangerous increases in core temperature. However, relative to young adults, healthy active adults ≥40 years of age (63) and individuals with diabetes (64,65) have a restricted capacity to lose heat. This is a result of reductions in the heat loss responses of sweating and skin blood flow, which occur even during short duration and/or light-to-moderate intensity exercise (63,66–70). Reduced physical fitness (70) and the presence of metabolic, CV and neurologic dysfunctions, which are often associated with diabetes (71), further exacerbate an already compromised ability to dissipate heat.

People with diabetes should be aware that heat stress is associated with a reduction in exercise capacity and an increase in disease-related symptoms (71). Combined with greater levels of dehydration due to hyperglycemia and/or medication use (71), individuals with type 2 diabetes have an augmented risk of heat-related morbidity. Whenever possible, exercise should be performed indoors in a cool and/or dry and well-ventilated environment (e.g. an air-conditioned training centre, room with fans) if it is very hot outdoors. If activities (e.g. gardening, cycling, etc.) must be performed outdoors when the weather is hot, the activities should be conducted in the early or later hours of the day when the temperatures are cooler and the sun is not at its peak. When possible, prolonged exercise (>15 min) should be interspersed with adequate rest or break periods in a shaded or cool location. Middle-aged and older people with diabetes should try to avoid performing exercise in hot humid conditions as these conditions restrict the evaporation of sweat which is necessary to cool the body. Staying well hydrated will help ensure that the body can maintain an adequate cooling capacity during exercise (by maintaining sweat production at normal levels) especially in the heat, and prevent fluctuations in blood glucose levels (71,72), and is likely to reduce the risk for heat-related complications, such as heat exhaustion or heat stroke.

Minimizing risk of exercise-induced hypoglycemia in type 1 diabetes

Prolonged aerobic exercise increases insulin sensitivity in recovery for up to 48 hours (73). In type 1 diabetes, there is little or no endogenous insulin secretion, and achieving the appropriate balance of exogenous insulin and carbohydrate intake for the different forms and intensities of exercise can be challenging (74). If exogenous insulin and/or carbohydrate ingestion is not adjusted accordingly, hypo- or hyperglycemia occurs. Fear of hypoglycemia is an important barrier to exercise in people with type 1 diabetes (75) and advice on physical activity to people with type 1 diabetes should include strategies to reduce risk of hypoglycemia.

Several small studies have explored several types of strategies for the prevention of hypoglycemia in type 1 diabetes, including the consumption of extra carbohydrates for exercise (76), limiting preprandial bolus insulin doses (77–79) or reducing the basal insulin rate for continuous subcutaneous insulin infusion (CSII) (insulin pump) users (80). These strategies can be used alone or in combination (81,82). Increasing carbohydrate intake just before, during and immediately after exercise is a simple and effective way to prevent hypoglycemia, although the optimal carbohydrate intake rate varies based on the duration and intensity of the activity and the amount of insulin in the circulation at the time of exercise (78,83,84). For activities less than 2 hours after a meal, reductions in prandial insulin by 25% to 75% are effective in limiting hypoglycemia (77). However, heavy reductions in mealtime insulin before (by 75%) and after exercise (by 50%) may cause hyperglycemia (85).

Basal insulin reduction before exercise may also offer some protection for children (86) and for those people on CSII (79,87). In 1 study, a 50% basal rate reduction performed 60 minutes before the onset of 30 minutes of moderate-intensity exercise does not reduce insulin level enough during the activity to adequately attenuate hypoglycemia risk (88). A more aggressive basal rate reduction, such as basal rate suspension at exercise onset is somewhat effective, although blood glucose levels may still drop markedly at the start of exercise (79). As such, additional carbohydrates may still be needed even following basal rate reductions. For people on insulin injections, in addition to lowering the mealtime bolus before exercise, exercise-associated hypoglycemia can be attenuated by reducing total daily basal insulin by 20% for days when they are physically active (89). Another strategy to avoid hypoglycemia is to perform intermittent, brief (10 seconds), maximal-intensity sprints either at the beginning (90) or end (91) or intermittently during a moderate-intensity exercise session (92). Performing resistance exercise immediately prior to aerobic exercise also helps reduce hypoglycemia risk, rather than performing aerobic exercise alone or aerobic exercise followed by resistance exercise (46).

Exercise performed late in the day or in the evening can be associated with increased risk of overnight hypoglycemia in people with type 1 diabetes (76). To reduce this risk, the bedtime intermediate or long-acting injected insulin dose, or overnight basal insulin infusion rate may be reduced by approximately 20% from bedtime to 3 AM for CSII users.

Minimizing risks related to hyperglycemia

Glucose levels can rise with brief intense exercise, such as sprinting (90–92), resistance training (93), 10 to 15 minutes of maximal-intensity aerobic exercise to exhaustion (94,95) or high-intensity interval training (96) in individuals with type 1 diabetes. If this occurs, it can be addressed by giving a small bolus of a rapid-acting insulin in exercise recovery (97), or by temporarily increasing the basal insulin infusion in CSII users.

Individuals with type 2 diabetes generally do not need to postpone exercise because of high blood glucose, provided they feel well. If capillary blood glucose levels are elevated >16.7 mmol/L, it is important to ensure proper hydration and monitor for signs and symptoms of dehydration (e.g. increased thirst, nausea, severe fatigue, blurred vision or headache), especially for exercise to be performed in the heat.

In individuals with type 1 diabetes who are severely insulin deficient (e.g. due to insulin omission or illness), hyperglycemia can worsen with exercise. In people with type 1 diabetes, if CBG is >16.7 mmol/L and the person does not feel well, urine or blood ketones should be tested. If ketone levels are elevated in the blood (≥1.5 mmol/L) or in the urine (2 + or ≥4 mmol/L), it is suggested that vigorous exercise be postponed until insulin is given (with carbohydrate, if necessary) and ketones are no longer elevated. If ketones are negative or “trace” and the person feels well, it is not necessary to defer exercise due to hyperglycemia.

Reduction of Sedentary Behaviour

Sedentary behaviours involve prolonged sitting or reclining while awake, including television viewing, working on a computer and driving. Systematic reviews of observational studies (98,99) have demonstrated positive associations between the amount of sitting and the risk of premature mortality within the general population and in people with diabetes (100,101) even after adjusting for time spent in moderate-to-vigorous physical activity (98–101). Several recent studies in people with diabetes have documented harmful associations between objectively measured sedentary time and cardiometabolic risk factors, such as A1C, central adiposity, BMI, fasting TG, systolic BP, C-reactive protein, and hyperglycemia (102–107). Studies in people with and without type 2 diabetes have demonstrated that interrupting sitting by light walking or light resistance training can attenuate postprandial increases in BG, insulin and TG (108–110).

Given the evidence that sedentary behaviour is associated with adverse health outcomes, even after statistically adjusting for levels of moderate-to-vigorous exercise, physical activity levels and sedentary behaviours should be considered distinct and potentially independent behaviours. When discussing activity patterns with people with diabetes in clinical practice, it is reasonable, therefore, to promote both the reduction of prolonged sitting and the accumulation of moderate-to-vigorous physical activity in the person's daily routine.

The Use of Adjunct Motivational Interventions to Improve Physical Activity Uptake

There are a number of barriers and facilitators to physical activity in people with diabetes (111–114). Interventions targeting these barriers and facilitators are needed to initially engage people with diabetes in, and then maintain, sufficient physical activity.

Behaviour-change focused interventions added to exercise-based interventions have tended to focus on increasing physical activity self-efficacy (i.e. an individual's belief or confidence in his/her ability to undertake physical activity) (115) and motivation (i.e. an individual's desire or willingness to do physical activity) (116). Such interventions have been shown to increase self-reported and/or objectively assessed physical activity when compared to usual care or equivalent comparison groups (115,117–122), although it is unclear if these improvements in physical activity are associated with improved A1C. For example, a recent meta-analysis suggested that the use of motivational interviewing-based interventions (see description below) not only improved physical activity but also decreased A1C by about 0.65% 6 months after the intervention when compared to usual care (119). However, it should be noted that some other studies found this kind of intervention did not reduce A1C (123,124).

The vast majority of the studies have examined motivational interviewing (125) or motivational communication (126) as the behaviour change intervention. Motivational interviewing is a goal-oriented, client-centred counselling style, which helps to explore and resolve ambivalence and increase intrinsic motivation in individuals in order to change behaviour (125). Motivational communication represents a collection of evidence-based strategies drawn from motivational interviewing, cognitive-behavioural techniques and behaviour change theories (e.g. self-determination theory, social-cognitive theory, theory of planned behaviour and the transtheoretical model) that are used as a communication strategy to engage individuals in changing their behaviour (126).

For people with type 2 diabetes, evidence suggests that goal setting, problem solving, providing information on where and when to exercise, and self-monitoring (e.g. use of objective monitoring with pedometers) have some efficacy to increase physical activity and improve A1C (114,127–131).

Newer evidence is starting to accumulate on the potential benefits of other motivational tools and techniques. Examples of these include reinforcement, such as providing direct, instantaneous rewards (monetary or token-based) for goal completion (132), text-messaging (133,134), mobile applications, social media and video games (116,135). However, further higher level evidence is needed to demonstrate their benefits for both physical activity and diabetes-related outcomes (129,136–138).

Objective Monitoring of Physical Activity

A pedometer is a wearable device that detects and counts each step a person takes. An accelerometer is a device that measures non-gravitational acceleration. Pedometers and accelerometers are well suited to measuring walking or jogging, but not bicycling or swimming. Pedometers measure steps but not speed, whereas accelerometers can measure both steps and speed.

Large-scale cohort studies consistently demonstrate an inverse relationship between higher self-reported walking with CV events and both CV and all-cause mortality in type 2 diabetes, even with adjustments for other CV risk factors. In a cohort analysis (9,306 participants in 40 countries) in people with prediabetes (139), 2,000 more steps/day at baseline was associated with a 10% reduction in CVD events at a median of 6 years and increasing counts by 2,000 steps/day in the first year of follow up was associated with an 8% reduction in CVD event rates at 6 years.

In a randomized controlled trial examining the effect of a pedometer-based prescription in people with type 2 diabetes, the change in A1C at the end of the 1-year step count prescription intervention was 0.38% lower in the active arm compared to the control arm (140). Active arm participants reviewed step count logs with their physicians at each clinic visit over a 1-year period, set step targets and received a written step count prescription. Those in the control arm were encouraged to be active 30 to 60 minutes daily. The change in steps over the 1-year intervention was 1,200 steps/day higher in the active compared to the control arm (140) (see Appendix 4. Smarter Step Count Prescription).

Two meta-analyses of clinical trials in type 2 diabetes demonstrated that pedometer-based facilitator-led group programs increase step counts by about 2,000 steps/day over 3 to 6 months (141,142). In these trials, the active arms engaged in pedometer-based interventions with monitoring and recording of daily step counts often complemented by support from a facilitator with or without peers in a group.

Exercise Prescription Examples

The following are practical examples illustrating how exercise can be prescribed:

Aerobic exercise

- Start by walking at a comfortable pace for as little as 5 to 15 minutes at one time.
- Gradually progress over 12 weeks to up to 50 minutes per session (including warm-up and cool down) of brisk walking.
- Alternatively, shorter exercise sessions in the course of a day, e.g. 10 minutes 3 times a day after meals, can replace a single longer session of equivalent length and intensity (143) (Table 2).

Resistance exercise

- Choose approximately 6 to 8 exercises that target the major muscle groups in the body.

Table 2
Aerobic exercise

Definition and recommended frequency	Intensity	Examples
Rhythmic, repeated and continuous movements of the same large muscle groups for at least 10 minutes at a time.	Moderate: 64%–76% of person's maximum heart rate	• Biking • Brisk walking • Continuous swimming • Dancing • Raking leaves • Water aerobics
Moderate-to-vigorous intensity aerobic exercise is recommended for a minimum of 150 minutes per week, no more than 2 consecutive days without exercise. Performance of smaller amounts of exercise is also beneficial, but to a lesser extent than the recommended amount. Higher-intensity interval training can increase aerobic fitness gains compared to continuous moderate-intensity exercise	Vigorous: >76% of person's maximum heart rate	• Brisk walking up an incline • Jogging • Aerobics • Hockey

Table 3
Resistance exercise*

Definition	Recommended frequency	Examples
Activities of brief duration involving the use of weights, weight machines or resistance bands to increase muscle strength and endurance	**2–3 times per week** • Start with 1 set using a weight with which you can perform 15 to 20 repetitions while maintaining proper form. • Progress to 2 sets and decrease the number of repetitions to 10–15 while increasing the weight slightly. If you cannot complete the required repetitions while maintaining proper form, reduce the weight. • Progress to 3 sets of 8 repetitions performed using an increased weight, ensuring proper form is maintained.	• Exercise with weight machines • Exercise with free weights

* Initial instruction and periodic supervision are recommended.
Note: The evidence supporting exercise with resistance bands is not as strong as the evidence for free weights or weight machines.

- Gradually increase the resistance until you can perform 3 sets of 8 to 12 repetitions for each exercise, with 1 to 2 minutes of rest between sets (113).
- The best evidence supports strength training with weight machines or free weights. Resistance bands may not be as effective to improve glycemic control, but they can help increase strength and can be a starting point to progress to other forms of resistance training.
- If you wish to begin resistance exercise, you should receive initial instruction and periodic supervision by a qualified exercise specialist to maximize benefits, while minimizing risk of injury, at least for the initial sessions (Table 3).

Interval exercise

- Exercise performed in intervals, alternating between higher intensity and lower intensity, can be used by participants who have trouble sustaining continuous aerobic exercise, or can be used to shorten total exercise duration or increase variety. Try alternating between 3 minutes of faster walking and 3 minutes of slower walking (144).
- Another form of interval training, high-intensity interval training (HIIT), can be performed through shorter intervals of higher-intensity exercise (e.g. 30 seconds to 1 minute at near-maximal intensity alternating with 1–3 minutes of lower-intensity activity) and can be performed with walking/running or other modalities, such as stationary cycling (8,26).
- Start with just a few intervals and progress to longer durations by adding additional intervals.

Other types of exercise

- Aquatic exercise can have similar benefits as other forms of exercise and help minimize barriers from conditions, such as osteoarthritis. Aquatic exercise can include walking briskly in the water, swimming or classes that include a variety of exercises.
- Other types of exercise or exercise classes, such as yoga, may be appealing for reasons, such as stress management.

Using pedometers or accelerometers

- Encourage people with diabetes to self-monitor physical activity with a pedometer or accelerometer. Ask them to record values, review at visits, set step count targets and formalize recommendations with a written prescription (see Appendix 4. Smarter Step Count Prescription).

Breaking up sedentary time

- It is best to avoid prolonged sitting. Try to interrupt sitting time by getting up briefly every 20 to 30 minutes.

Physical Activity in Children with Type 2 Diabetes: see Type 2 Diabetes in Children and Adolescents chapter, p. S247.

RECOMMENDATIONS

1. People with diabetes should ideally accumulate a minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise, to improve glycemic control [Grade B, Level 2, for adults with type 2 diabetes (2,4,6) and children with type 1 diabetes (20)]; and to reduce risk of CVD and overall mortality [Grade C, Level 3, for adults with type 1 diabetes (14) and type 2 diabetes (10)]. Smaller amounts (90–140 minutes/week) of exercise or planned physical activity can also be beneficial but to a lesser extent [Grade B, Level 2 (6,7) for glycemic control in type 2 diabetes; Grade C, Level 3 for mortality in type 2 diabetes (10) and type 1 diabetes (14)].

2. Interval training (short periods of vigorous exercise alternating with short recovery periods at low-to-moderate intensity or rest from 30 seconds to 3 minute each) can be recommended to people willing and able to perform it to increase gains in cardiorespiratory fitness in type 2 diabetes [Grade B, Level 2 (144)] and to reduce risk of hypoglycemia during exercise in type 1 diabetes [Grade C, Level 3 (28,29)].

3. People with diabetes (including elderly people) should perform resistance exercise at least twice a week (39) and preferably 3 times per week [Grade B, Level 2 (30)] in addition to aerobic exercise [Grade B, Level 2 (39–42)]. Initial instruction and periodic supervision by an exercise specialist can be recommended [Grade C, Level 3 (30)].

4. In addition to achieving physical activity goals, people with diabetes should minimize the amount of time spent in sedentary activities and periodically break up long periods of sitting [Grade C, Level 3 (100)].

5. Setting specific exercise goals, problem solving potential barriers to physical activity, providing information on where and when to exercise, and self-monitoring should be performed collaboratively between the person with diabetes and the health-care provider to increase physical activity and improve A1C [Grade B, Level 2 (128,129)].

6. Step count monitoring with a pedometer or accelerometer can be considered in combination with physical activity counselling, support and goal-setting to support and reinforce increased physical activity [Grade B, Level 2 (140,141)].

7. To reduce risk of hypoglycemia during and after exercise in people with type 1 diabetes, the following strategies can be considered alone or in combination:
   a. Reduce the bolus dose of the insulin that is most active at the time of exercise [Grade B, Level 2 (85)]
   b. Significantly reduce, or suspend (only if the activity is ≤45 minutes), basal insulin for the exercise duration [Grade B, Level 2 (79,87)], and lower the basal rate overnight after exercise by ~20% [Grade B, Level 2 (86)]
   c. Increase carbohydrate consumption prior to, during and after exercise, as necessary [Grade C, Level 3 (78,83,84)]
   d. Perform brief (10 seconds), maximal-intensity sprints at the start of exercise [Grade D, Level 4 (90)], periodically during the activity [Grade D, Level 4 (92)], or at the end of exercise [Grade D, Level 4 (91)]
   e. Perform resistance exercise before aerobic exercise [Grade D, Level 4 (46)].

8. People with diabetes ≥40 years of age who wish to undertake very vigorous or prolonged exercise, such as competitive running, long-distance running, or high-intensity interval training, should be assessed for conditions that might place them at increased risk for an adverse event with history, physical examination (including fundoscopic exam, foot exam and neuropathy screening), resting ECG and, possibly, exercise ECG stress testing [Grade D, Consensus].

9. Structured exercise programs supervised by qualified trainers should be implemented when feasible for people with type 2 diabetes to improve glycemic control, CV risk factors and physical fitness [Grade B, Level 2 (6,39)].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *BP*, blood pressure; *BMI*, body mass index; *CV*, cardiovascular; *CVD*, cardiovascular disease; *ECG*, electrocardiogram; *FPG*, fasting plasma glucose; *HDL-C*; high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol.

Other Relevant Guidelines

Monitoring Glycemic Control, p. S47
Glycemic Management in Adults with Type 1 Diabetes, p. S80
Hypoglycemia, p. S104
Screening for the Presence of Cardiovascular Disease, p. S170
Type 2 Diabetes in Children and Adolescents, p. S247

Relevant Appendix

Appendix 4. Smarter Step Count Prescription

Author Disclosures

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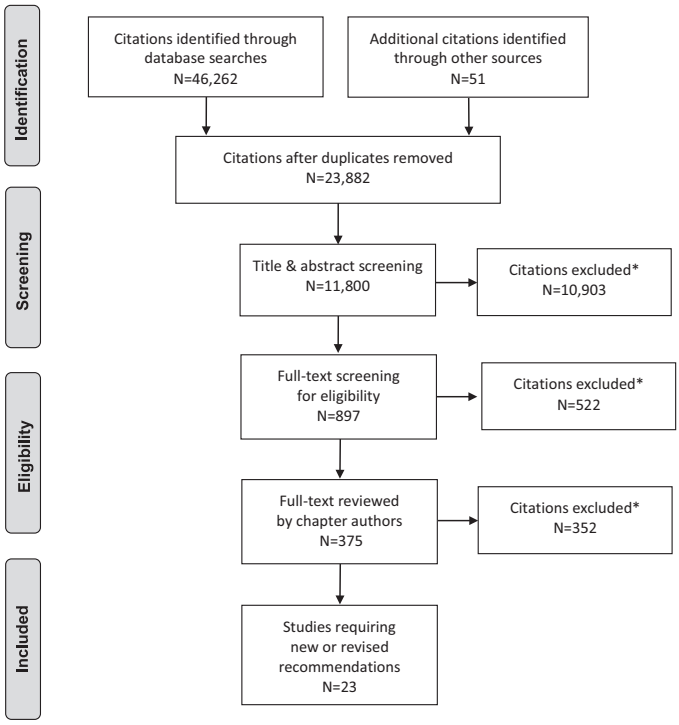
Literature Review Flow Diagram for Chapter 10: Physical Activity and Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (145).

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2018 Clinical Practice Guidelines

Nutrition Therapy

Diabetes Canada Clinical Practice Guidelines Expert Committee

John L. Sievenpiper MD, PhD, FRCPC, Catherine B. Chan PhD, Paula D. Dworatzek PhD, RD, Catherine Freeze MEd, RD, CDE, Sandra L. Williams MEd, RD, CDE

KEY MESSAGES

- People with diabetes should receive nutrition counselling by a registered dietitian.
- Nutrition therapy can reduce glycated hemoglobin (A1C) by 1.0% to 2.0% and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes.
- Reduced caloric intake to achieve and maintain a healthier body weight should be a treatment goal for people with diabetes with overweight or obesity.
- The macronutrient distribution is flexible within recommended ranges and will depend on individual treatment goals and preferences.
- Replacing high-glycemic-index carbohydrates with low-glycemic-index carbohydrates in mixed meals has a clinically significant benefit for glycemic control in people with type 1 and type 2 diabetes.
- Consistency in spacing and intake of carbohydrate intake and in spacing and regularity in meal consumption may help control blood glucose and weight.
- Intensive healthy behaviour interventions in people with type 2 diabetes can produce improvements in weight management, fitness, glycemic control and cardiovascular risk factors.
- A variety of dietary patterns and specific foods have been shown to be of benefit in people with type 1 and type 2 diabetes.
- People with diabetes should be encouraged to choose the dietary pattern that best aligns with their values, preferences and treatment goals, allowing them to achieve the greatest adherence over the long term.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- It is natural to have questions about what food to eat. A registered dietitian can help you develop a personalized meal plan that considers your culture and nutritional preferences to help you achieve your blood glucose and weight management goals.
- Food is key in the management of diabetes and reducing the risk of heart attack and stroke.
- Try to prepare more of your meals at home and use fresh unprocessed ingredients.
- Try to prepare meals and eat together as a family. This is a good way to model healthy food behaviours to children and teenagers, which could help reduce their risk of becoming overweight or developing diabetes.
- With prediabetes and recently diagnosed type 2 diabetes, weight loss is the most important and effective dietary strategy if you have overweight or obesity. A weight loss of 5% to 10% of your body weight may help normalize blood glucose levels.
- There are many strategies that can help with weight loss. The best strategy is one that you are able to maintain long term.
- Adoption of diabetes-friendly eating habits can help manage your blood glucose levels as well as reduce your risk for developing heart and blood vessel disease for those with either type 1 or type 2 diabetes.
  - Select whole and less refined foods instead of processed foods, such as sugar-sweetened beverages, fast foods and refined grain products.
  - Pay attention to both carbohydrate quality and quantity.
  - Include low-glycemic-index foods, such as legumes, whole grains, and fruit and vegetables. These foods can help control blood glucose and cholesterol levels.
  - Consider learning how to count carbohydrates as the quantity of carbohydrate eaten at one time is usually important in managing diabetes.
  - Select unsaturated oils and nuts as the preferred dietary fats.
  - Choose lean animal proteins. Select more vegetable protein.
  - The style of eating that works well for diabetes may be described as a Mediterranean style diet, Nordic style diet, DASH diet or vegetarian style diet. All of these diets are rich in protective foods and have been shown to help manage diabetes and cardiovascular disease. They all contain the key elements of a diabetes-friendly diet.

Introduction

Nutrition therapy and counselling are an integral part of the treatment and self-management of diabetes. The goals of nutrition therapy are to maintain or improve quality of life and nutritional and physiological health; and to prevent and treat acute- and long-term complications of diabetes, associated comorbid conditions and concomitant disorders. It is well documented that nutrition therapy can improve glycemic control (1) by reducing glycated hemoglobin (A1C) by 1.0% to 2.0% (2–5) and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes (3,4,6,7), resulting in reduced hospitalization rates (8).

Ethnocultural Diversity

Canada is a country rich in ethnocultural diversity. More than 200 ethnic origins were reported in Canada in the 2011 census. The most common ethnic origins with populations in excess of 1 million from highest to lowest include Canadian, English, French, Scottish, Irish, German, Italian, Chinese, Aboriginal, Ukrainian, East Indian, Dutch and Polish. The largest visible minorities include South Asians, Chinese and Blacks, followed by Filipinos, Latin Americans, Arabs, Southeast Asians, West Asians, Koreans and Japanese (9). These different ethnocultural groups have distinct and shared foods, food preparation techniques, dining habits, dietary patterns, and lifestyles that directly impact the delivery of nutrition therapy. A

Conflict of interest statements can be found on page S74.

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"transcultural" approach to nutrition therapy that takes into account these issues has been proposed and has the goal of providing culturally congruent nutrition counselling (10).

Approach to Nutrition Therapy

Nutrition therapy should be individualized, regularly evaluated, reinforced in an intensive manner (11,12), and should incorporate self-management education (13). A registered dietitian (RD) should be involved in the delivery of care wherever possible. Counselling provided by an RD with expertise in diabetes management (14,15), delivered in either a small group and/or an individual setting (16–18), has demonstrated benefits for those with, or at risk for, diabetes. Frequent follow up (i.e. every 3 months) with an RD has also been associated with better dietary adherence in people with type 2 diabetes (7). Individual counselling may be preferable for people of lower socioeconomic status (8), while group education has been shown to be more effective than individual counselling when it incorporates principles of adult education (19). Additionally, in people with type 2 diabetes, culturally sensitive peer education has been shown to improve A1C, nutrition knowledge and diabetes self-management (20), and web-based care management has been shown to improve glycemic control (21). Diabetes education programs serving vulnerable populations should evaluate the presence of barriers to healthy eating (e.g. cost of healthy food, stress-related overeating) (22) and work toward solutions to facilitate behaviour change.

The starting point of nutrition therapy is to follow the healthy diet recommended for the general population based on *Eating Well With Canada's Food Guide* (22). As the Food Guide is in the process of being updated, specific recommendations are subject to change based on the evidence review and public consultation by Health Canada (https://www.foodguideconsultation.ca/professionals-and-organizations). Current dietary advice is to consume a variety of foods from the 4 food groups (vegetables and fruits; grain products; milk and alternatives; meat and alternatives), with an emphasis on foods that are low in energy density and high in volume to optimize satiety and discourage overconsumption. Following this advice may help a person attain and maintain a healthy body weight while ensuring an adequate intake of carbohydrate (CHO), fibre, fat, protein, vitamins and minerals.

There is evidence to support a number of other macronutrient-, food- and dietary pattern-based approaches. As evidence is limited for the rigid adherence to any single dietary approach (23,24), nutrition therapy and meal planning should be individualized to accommodate the individual's values and preferences, which take into account age, culture, type and duration of diabetes, concurrent medical therapies, nutritional requirements, lifestyle, economic status (25), activity level, readiness to change, abilities, food intolerances, concurrent medical therapies and treatment goals. This individualized approach harmonizes with that of other clinical practice guidelines for diabetes and for dyslipidemia (10,26).

Figures 1 and 2, and Table 1 present an algorithm that summarizes the approach to nutrition therapy for diabetes, applying the evidence from the sections that follow, and allowing for the individualization of therapy in an evidence-based framework.

Energy

Because an estimated 80% to 90% of people with type 2 diabetes have overweight or obesity, strategies that include energy restriction to achieve weight loss are a primary consideration (27). A modest weight loss of 5% to 10% of initial body weight can substantially improve insulin sensitivity, glycemic control, hypertension and dyslipidemia in people with type 2 diabetes and those at risk for type 2 diabetes (28–30). Total calories should reflect the weight management goals for people with diabetes and overweight or obesity (i.e. to prevent further weight gain, to attain and maintain a healthy or lower body weight for the long term or to prevent weight regain).

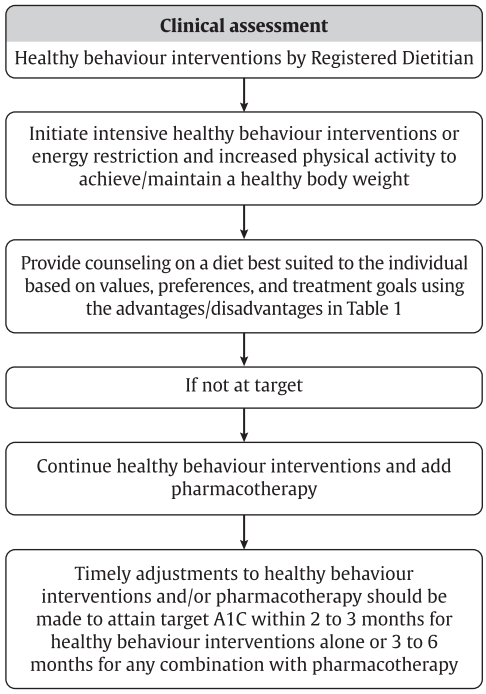

Figure 1. Nutritional management of hyperglycemia in type 2 diabetes. *A1C*, glycated hemoglobin.

Macronutrients

The ideal macronutrient distribution for the management of diabetes may vary, depending on the quality of the various macronutrients, the goals of the dietary treatment regimen and the individual's values and preferences.

Carbohydrate

CHO broadly include available CHO from starches and sugars and unavailable CHO from fibre. The dietary reference intakes (DRIs) specify a recommended dietary allowance (RDA) for available CHO of no less than 130 g/day for adult women and men >18 years of age, to provide glucose to the brain (31). The DRIs also recommended that the percentage of total daily energy from CHO should be ≥45% to prevent high intake of saturated fatty acids as it has been associated with reduced risk of chronic disease for adults (31). If CHO is derived from low glycemic index (GI) and high-fibre foods, it may contribute up to 60% of total energy, with improvements in glycemic and lipid control in adults with type 2 diabetes (32).

Systematic reviews and meta-analyses of controlled trials of CHO-restricted diets (mean CHO of 4% to 45% of total energy per day) for people with type 2 diabetes have not shown consistent improvements in A1C compared to control diets (33–35). Similarly, inconsistent improvements in lipids and blood pressure (BP) have been reported when comparing low-CHO to higher-CHO diets (33–35). As for weight loss, low-CHO diets for people with type 2 diabetes have not shown significant advantages for weight loss over the short term (33,34). There also do not appear to be any longer-term

Table 1
Properties of dietary interventions*†‡

Properties of dietary interventions (listed in the order they are presented in the text)				
Dietary interventions	**A1C**	**CV benefit**	**Other advantages**	**Disadvantages**
Macronutrient-based approaches				
Low-glycemic-index diets	↓ (32,44,46,47)	↓CVD (52)	↓LDL-C, ↓CRP, ↓hypoglycemia, ↓diabetes Rx	None
High-fibre diets	↓ (viscous fibre) (57)	↓CVD (69)	↓LDL-C, ↓non-HDL-C, ↓apo B (viscous fibre) (54,57,59)	GI side effects (transient)
High-MUFA diets	↔	↓CVD	↓Weight, ↓TG, ↓BP	None
Low-carbohydrate diets	↔	-	↓TG	↓Micronutrients, ↑renal load
High-protein diets	↓	-	↓TG, ↓BP, preserve lean mass	↓Micronutrients, ↑renal load
Mediterranean dietary pattern	↓ (50,139)	↓CVD (143)	↓retinopathy (144), ↓BP, ↓CRP, ↑HDL-C (139,140)	None
Alternate dietary patterns				
Vegetarian	↓ (145,251)	↓CHD (152)	↓Weight (148), ↓LDL-C (149)	↓vitamin B12
DASH	↓ (159)	↓CHD (161)	↓Weight (159), ↓LDL-C (159), ↓BP (159), ↓CRP (160)	None
Portfolio	-	↓CVD (162,163)	↓LDL-C (162,163), ↓CRP (162), ↓BP (163)	None
Nordic	-	-	↓LDL-C+, ↓non-HDL-C (169–171)	None
Popular weight loss diets				
Atkins	↔	-	↓Weight, ↓TG, ↑HDL-C, ↓CRP	↑LDL-C, ↓micronutrients, ↓adherence
Protein Power Plan	↓	-	↓Weight, ↓TG, ↑HDL-C	↓Micronutrients, ↓adherence, ↑renal load
Ornish	-	-	↓Weight, ↓LDL-C, ↓CRP	↔ FPG, ↓adherence
Weight Watchers	-	-	↓Weight, ↓LDL-C, ↑HDL-C, ↓CRP	↔ FPG, ↓adherence
Zone	-	-	↓Weight, ↓LDL-C, ↓TG, ↑HDL-C	↔ FPG, ↓adherence
Dietary patterns of specific foods				
Dietary pulses/legumes	↓ (176)	↓CVD (181)	↓Weight (179), ↓LDL-C (177), ↓BP (178)	GI side effects (transient)
Fruit and vegetables	↓ (183,184)	↓CVD (79)	↓BP (186,187)	None
Nuts	↓ (188)	↓CVD (143,181)	↓LDL-C (190), ↓TG, ↓FPG (189)	Nut allergies (some individuals)
Whole grains	↓ (oats) (194)	↓CHD (99)	↓LDL-C, FPG (oats, barley) (57,193)	GI side effects (transient)
Dairy	↔	↓CVD (199,200)	↓BP, ↓TG (when replacing SSBs) (197)	Lactose intolerance (some individuals)
Meal replacements	↓	-	↓Weight	Temporary intervention

* ↓ = <1% decrease in A1C.
† Adjusted for medication changes.
‡ References are for the evidence used to support accompanying recommendations.
A1C, glycated hemoglobin; *apo B*, apolipoprotein B; *BMI*, body mass index; *BP*, blood pressure; *CHD*, coronary heart disease; *CHO*, carbohydrate; *CRP*, C reactive protein; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DASH*, Dietary Approaches to Stop Hypertension; *FPG*, fasting plasma glucose; *GI*, gastrointestinal; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *MUFA*, monounsaturated fatty acid; *SSBs*, sugar-sweetened beverages; *TC*, total cholesterol; *TG*, triglycerides.

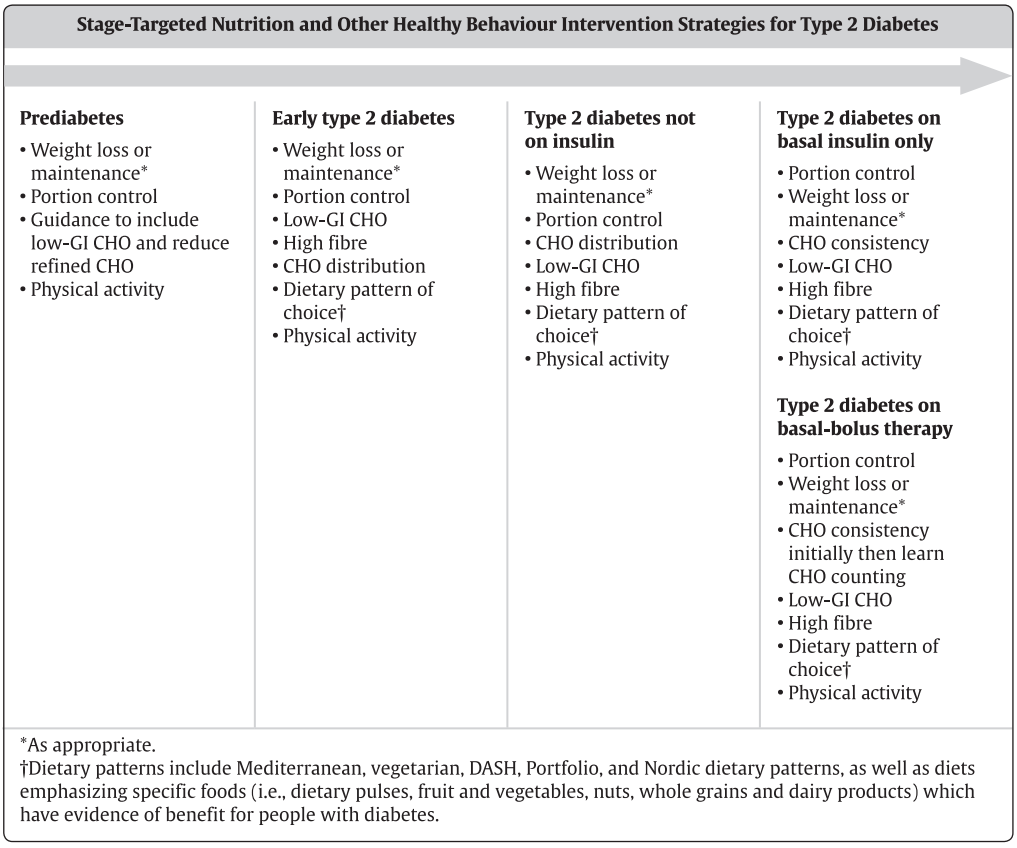

Figure 2. Stage-targeted nutrition and other healthy behaviour strategies for people with type 2 diabetes.
CHO, carbohydrate; *GI*, glycemic index; *NPH*, neutral protamine Hagedorn.

advantages. Although a network systematic review and meta-analysis of randomized controlled trials of popular weight loss diets showed that low-CHO diets (defined as ≤40% energy from CHO) resulted in greater weight loss compared with high-CHO, low-fat diets (defined as ≥60% energy from CHO) at 6 months, there was no difference at 12 months in individuals with overweight or obesity with a range of metabolic phenotypes, including type 2 diabetes (36). Of note, very-low-CHO diets have ketogenic effects that may be a concern for those at risk of diabetic ketoacidosis taking insulin or SGLT2 inhibitors (37) (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88).

A limited number of small, short-term studies conducted on the use of low-CHO diets (target <75 g/day) in people with type 1 diabetes have demonstrated modest adherence to the prescribed diets with improved A1C for those who can adhere. This style of diet can be an option for those motivated to be so restrictive (38,39). Of concern for those following a low-CHO diet is the effectiveness of glucagon in the treatment of hypoglycemia. In a small study, people with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII) therapy following a low-CHO diet for 1 week had a blunted response to a glucagon bolus (40,41). The long-term sustainability and safety of these diets remains uncertain.

Glycemic Index

The glycemic index (GI) provides an assessment of the quality of CHO-containing foods based on their ability to raise blood glucose (BG) (42). To decrease the glycemic response to dietary intake, low-GI CHO foods are exchanged for high-GI CHO foods. Detailed lists can be found in the *International Tables of Glycemic Index and Glycemic Load Values* (43).

Systematic reviews and meta-analyses of randomized trials and large individual randomized trials of interventions replacing high-GI foods with low-GI foods have shown clinically significant improvements in glycemic control over 2 weeks to 6 months in people with type 1 or type 2 diabetes (44–51). This dietary strategy has also been shown to improve postprandial glycemia and reduce high-sensitivity C-reactive protein (hsCRP) over 1 year in people with type 2 diabetes (48), reduce the number of hypoglycemic events over 24 to 52 weeks in adults and children with type 1 diabetes (47) and improve total cholesterol (TC) over 2 to 24 weeks in people with and without diabetes (46). Irrespective of the comparator, recent systematic reviews and meta-analyses have confirmed the beneficial effect of low-GI diets on glycemic control and blood lipids in people with diabetes (49–51). Other lines of evidence extend these benefits. A systematic review and meta-analysis of prospective cohort studies inclusive of people with diabetes showed that high GI and high glycemic load (GL) diets are associated with increased incidence of cardiovascular disease (CVD), when comparing the highest with the lowest exposures of GI and GL in women more than men over 6 to 25 years (52).

Dietary fibre

Dietary fibre includes the edible components of plant material that are resistant to digestion by human enzymes (nonstarch polysaccharides and lignin, as well as associated substances). They include fibres from commonly consumed foods as well as accepted novel fibres that have been synthesized or derived from agricultural by-products (53). DRIs specify an adequate intake (AI) for total fibre of 25 g/day and 38 g/day for women and men 19–50 years of age, respectively, and 21 g/day and 30 g/day for women and men ≥51 years of age, respectively (31). Although these recommendations do not differentiate between insoluble and soluble fibres or viscous and nonviscous fibres within soluble fibre, the evidence supporting metabolic benefit is greatest for viscous soluble fibre from different plant sources (e.g. beta-glucan from oats and barley, mucilage from psyllium, glucomannan from konjac mannan, pectin from dietary pulses, eggplant, okra and temperate climate fruits (apples, citrus fruits, berries, etc.). The addition of viscous soluble fibre has been shown to slow gastric emptying and delay the absorption of glucose in the small intestine, thereby improving postprandial glycemic control (54,55).

Systematic reviews, meta-analyses of randomized controlled trials and individual randomized controlled trials have shown that different sources of viscous soluble fibre result in improvements in glycemic control assessed as A1C or fasting blood glucose (FBG) (56–58) and blood lipids (59–61). A lipid-lowering advantage is supported by Health Canada-approved cholesterol-lowering health claims for the viscous soluble fibres from oats, barley and psyllium (62–64).

Despite contributing to stool bulking (65), insoluble fibre has failed to show similar metabolic advantages in randomized controlled trials in people with diabetes (56,66,67). These differences between soluble and insoluble fibre are reflected in the EURODIAB prospective complications study, which demonstrated a protective association of soluble fibre that was stronger than that for insoluble fibre in relation to nonfatal CVD, cardiovascular (CV) mortality and all-cause mortality in people with type 1 diabetes (68). However, this difference in the metabolic effects between soluble and insoluble fibre is not a consistent finding. A recent systematic review and meta-analysis of prospective cohort studies in people with and without diabetes did not show a difference in risk reduction between fibre types (insoluble, soluble) or fibre source (cereal, fruit, vegetable) (69). Given this inconsistency, mixed sources of fibre may be the ideal strategy. Interventions emphasizing high intakes of dietary fibre (≥20 g/1,000 kcal per day) from a combination of types and sources with a third or more provided by viscous soluble fibre (10 to 20 g/day) have shown important advantages for postprandial BG control and blood lipids, including the established therapeutic lipid target low-density lipoprotein cholesterol (LDL-C) (54,58,70) and, therefore, emphasizing fibre from mixed sources may help to ensure benefit.

Sugars

Added sugars, especially from fructose-containing sugars (high fructose corn syrup [HFCS], sucrose and fructose), have become a focus of intense public health concern. The main metabolic disturbance of fructose and sucrose in people with diabetes is an elevation of fasting triglycerides (TG) at doses >10% of total daily energy. A systematic review and meta-analysis of randomized controlled trials ≥2-weeks duration showed that added sugars from sucrose, fructose and honey in isocaloric substitution for starch have a modest fasting TG-raising effect in people with diabetes, which was not seen at doses ≤10% of total energy (71). Fructose-containing sugars either in isocaloric substitution for starch or under ad libitum conditions have not demonstrated an adverse effect on lipoproteins (LDL-C, TC, high-density lipoprotein cholesterol [HDL-C]), body weight or markers of glycemic control (A1C, FBG or fasting blood insulin) (71–73). Similar results have been seen for added fructose. Consumption of added fructose alone, in place of equal amounts of other sources of CHO (mainly starch), does not have adverse effects on body weight (74,75), BP (76), fasting TG (77,78), postprandial TG (79), markers of fatty liver (80) or uric acid (75,81). In fact, it may even lower A1C (75,82,83) in most people with diabetes. Although HFCS has not been formally tested in controlled trials involving people with diabetes, there is no reason to expect that it would give different results than sucrose. Randomized controlled trials of head-to-head comparisons of HFCS vs. sucrose at doses from the 5th to 95th percentile of United States population intake have shown no differences between HFCS and sucrose over a wide range of

cardiometabolic outcomes in participants with overweight or obesity without diabetes (84–87).

Food sources of sugars may be a more important consideration than the type of sugar per se. A wide range of studies including people with and without diabetes have shown an adverse association of sugar-sweetened beverages (SSBs) with risk of hypertension and coronary heart disease when comparing the highest with the lowest levels of intake (88,89). These differences are most apparent when SSBs account for more than 10% of total energy and are likely mediated by the excess calories (88,89). This adverse relationship may be specific to SSBs as the same adverse relationship has not been shown for total sugars, sucrose, or fructose (90–97), fructose-containing sugars from fruit (79,98) or food sources of added sugars, such as whole grains and dairy products (yogurt) (98–101).

Fat

The DRIs do not specify an AI or RDA for total fat, monounsaturated fatty acids (MUFA), saturated fatty acids (SFA), or dietary cholesterol. AIs have only been set for the essential polyunsaturated fatty acids (PUFA): 12 g and 11 g per day for women and 17 g and 14 g per day for men aged 19-50 years and >51 years, respectively, for the n-6 PUFA linoleic acid and 1.1 g per day for women and 1.6 g per day for men aged >18 years for the n-3 PUFA alpha-linolenic acid (31). The quality of fat (type of fatty acids) has been shown to be a more important consideration than the quantity of fat for CV risk reduction. Dietary strategies have tended to focus on the reduction of saturated fatty acids (SFA) and dietary cholesterol. The prototypical diets are the United States National Cholesterol Education Program (NCEP) Step I (≤30% total energy as fat, ≤10% of energy as SFA) and Step II (≤7% of energy as SFA, dietary cholesterol ≤200 mg/day) diets (102). These diets have shown improvements in lipids and other CV risk factors compared with higher SFA and cholesterol control diets (103).

More recent analyses have assessed the relation of different fatty acids with CV outcomes. A systematic review and meta-analysis of prospective cohort studies inclusive of people with diabetes showed that diets low in trans fatty acids (TFA) are associated with less coronary heart disease (CHD) (104). Another systematic review and meta-analysis of randomized controlled clinical outcome trials involving people with and without diabetes showed that diets low in SFA decrease combined CV events (105). The benefit, however, was restricted to intakes of SFA <9% total energy and to the replacement of SFA with polyunsaturated fatty acids (PUFA) (105). Other analyses of the available clinical outcome trials suggest that the food sources of PUFA may even be more relevant with CV benefit restricted to mixed omega-3/omega-6 PUFA sources, such as soybean oil and canola oil (106). Pooled analyses of prospective cohort studies and large individual cohort studies also suggest that replacement of saturated fatty acids with high quality sources of monounsaturated fatty acids (MUFA) from olive oil, canola oil, avocado, nuts and seeds, and high quality sources of carbohydrates from whole grains and low GI index carbohydrate foods is associated with decreased incidence of CHD (107,108).

The food source of the saturated fatty acids being replaced, however, is another important consideration. Whereas adverse associations have been reliably established for meat as a food source of saturated fatty acids, the same has not been shown for some other food sources of saturated fatty acids (e.g. such as dairy products and plant fats from palm and coconut) (109).

A comprehensive review of long-chain omega-3 fatty acids (LC-PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oils did not show an effect on glycemic control (110). Large randomized clinical outcome trials of supplementation with omega-3 LC-PUFAs do not support their use in people with diabetes (111–113). The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial failed to show a CV or mortality benefit of supplementation with omega-3 LC-PUFA in 12,536 people with prediabetes or type 2 diabetes (112). Subsequent systematic reviews and meta-analyses of randomized trials involving more than 75,000 participants with and without diabetes have failed to show a CV benefit of supplementation with long chain omega-3 PUFAs (114). The Study of Cardiovascular Events in Diabetes (ASCEND) in 15,480 people with diabetes free of CV disease (clinicaltrials.gov registration number NCT00135226) will provide more data on the outcomes of supplementation with omega-3 LC-PUFA in people with diabetes.

Although supplementation with omega-3 LC-PUFA has not been shown to be beneficial, consumption of fish may be. Prospective cohort analyses have shown higher consumption of fish, ranging from 1 to 3 servings per month to ≥2 servings/week of oily fish, was associated with reductions in coronary artery disease (CAD) (115), diabetic chronic kidney disease (CKD) in type 2 diabetes (116) and less albuminuria in type 1 diabetes (117).

Protein

The DRIs specify a recommended dietary allowance (RDA) for protein of 0.8 g per kg body weight for adult men and women >18 years of age (31). There is no evidence that the usual protein intake for most individuals (1 to 1.5 g per kg body weight per day), representing 15% to 20% of total energy intake, needs to be modified for people with diabetes (118). However, this intake in grams per kg per day should be maintained or increased with energy-reduced diets.

Protein quality has been shown to be another important consideration. A systematic review and meta-analysis of randomized controlled trials showed that replacement of animal protein with sources of plant protein improved A1C, FPG and fasting insulin in people with type 1 and type 2 diabetes over a median follow up of 8 weeks (119).

People with diabetes who have CKD should target a level of intake that does not exceed the RDA of 0.8 g per kilogram body weight per day (31), which has been shown to reduce end stage renal disease and mortality in people with type 1 diabetes and CKD (120) and improve albuminuria and A1C in people with CKD in diabetes (121). When using a low-protein diet, harm due to malnutrition should not be ignored (122). Both the quantity and quality (high biological value) of protein intake must be optimized to meet requirements for essential amino acids, necessitating adequate clinical and laboratory monitoring of nutritional status in the individual with diabetes and CKD. Greater incorporation of plant sources of protein may also require closer monitoring of potassium as CKD progresses.

Macronutrient substitutions

The ideal macronutrient distribution for the management of diabetes can be individualized. Based on evidence for chronic disease prevention and adequacy of essential nutrients, the DRIs recommend acceptable macronutrient distribution ranges (AMDRs) for macronutrients as a percentage of total energy. These include 45% to 65% energy for CHO, 10% to 35% energy for protein and 20% to 35% energy for fat, with 5% to 10% energy derived from linoleic acid and 0.6% to 1.2% energy derived from alpha linolenic acid (31).

There may be a benefit of substituting fat as MUFA for carbohydrate (123). A systematic review and meta-analysis of randomized controlled trials found that MUFA in isocaloric substitution for CHO (mean replacement of ~14% energy with a dietary macronutrient composition of 40% energy CHO, 33% energy fat, and 17% energy protein) did not reduce A1C but did improve FPG, body weight, systolic BP, TG and HDL-C in people with type 2 diabetes over an average follow up of 19 weeks (123). Similarly, the replacement of refined high-GI CHO with MUFA (14.5% total energy)

or nuts (5% total energy) to affect a low glycemic load has been shown to improve A1C and lipids, including the established therapeutic lipid target LDL-C in people with type 2 diabetes over 3 months (124).

The effect of the replacement of fat with CHO depends on the quality of the CHO and the fat. Whereas the replacement of fat with refined high-GI CHO results in worsening of metabolic parameters in people with type 2 diabetes (125), the replacement of saturated fatty acids with low-GI CHO or whole grain sources is associated with decreased incident CHD in people with and without diabetes (107,108).

When protein is used to replace CHO, as in a high-protein diet, benefit has only been demonstrated when high-GI CHO are replaced. A 12-month randomized controlled trial in individuals with type 2 diabetes showed improved CV risk profile with a high-protein diet (30% energy protein, 40% energy CHO, 30% energy fat) vs. a high-CHO diet (15% energy protein, 55% energy CHO, 30% energy fat), in which the CHO were high GI. These differences were seen despite similar weight loss with normal renal function being maintained (126). In contrast, a 12-month randomized controlled trial comparing a high-protein diet (30% energy protein, 40% energy CHO, 30% energy fat) vs. a high-CHO low-GI diet (15% energy protein, 55% energy CHO, 30% energy fat) failed to show a difference between the diets (127). Rather, it was adherence to any 1 diet and the degree of energy restriction, not the variation in diet macronutrient composition, that was associated with the long-term improvement in glycemic control and cardiometabolic risk factors (127).

Adjustments in medication type and dosage may be required when embarking on a different macronutrient distribution (128) or energy reduction (129) to avoid hypoglycemia.

Intensive Lifestyle Intervention

Intensive lifestyle intervention (ILI) programs in diabetes usually consist of behavioural interventions combining dietary modification and increased physical activity. An interprofessional team, including registered dietitians, nurses and kinesiologists, usually leads the ILI programs, with the intensity of follow up varying from weekly to every 3 months with gradually decreasing contact as programs progress. Large, randomized clinical trials have shown benefit of ILI programs using different lifestyle approaches in diabetes. Twenty-year follow up of the China Da Qing Diabetes Prevention Outcome Study showed that 6 years of an ILI program targeting an increase in vegetable intake, decrease in alcohol and simple sugar intake, weight loss through energy restriction in participants with overweight or obesity, and an increase in leisure time physical activity (e.g. 30 minutes walking per day) reduced severe retinopathy by 47%, whereas nephropathy and neuropathy outcomes were not affected compared with usual care in high-risk people with impaired glucose tolerance (IGT) (130). After 23 years of follow up, the intervention group had a 41% reduction in CV mortality, 29% reduction in all cause-mortality and 45% reduction in progression to type 2 diabetes (131).

Analyses of the Look Action for Health in Diabetes (AHEAD) trial have shown that an ILI program targeting at least a 7% weight loss through a restriction in energy (1,200 to 1,800 total kcal/day based on initial weight), a reduction in fat (<30% of energy as total fat and <10% as saturated fat), an increase in protein (≥15% of energy) and an increase in physical activity (175 min/week with an intensity similar to brisk walking) produced sustained weight loss during 10 years follow up compared with diabetes support and education in persons with overweight and type 2 diabetes (132). However, it should be noted that analysis after 8 years showed that initial weight loss was attributable to reduction in both fat and lean mass, whereas weight regain was attributable only to fat mass, with continued decline in lean mass (133). Improvements in glycemic control and CV risk factors (BP, TG and HDL-C) were greatest at 1 year and diminished over time with the most sustainable reductions being in A1C, fitness and systolic BP (132). In 2012, the Look AHEAD trial was stopped early as it was determined that 11 years of an ILI did not decrease the occurrence of CV events compared to the control group and further intervention was unlikely to change this result. It was noted, however, that both groups had a lower number of CV events compared to previous studies of people with diabetes. Other studies of ILI have shown similar results (134,135).

Although the available trials suggest an overall short-term benefit of different ILI programs in people with diabetes, the feasibility of implementing an ILI program will depend on the availability of resources and access to an interprofessional team. Effects attenuate within 8 years and do not appear to provide lasting CV protection.

Dietary Patterns

A variety of dietary patterns have been studied for people with prediabetes and diabetes. An individual's values, preferences and treatment goals will influence the decision to use these dietary patterns.

Mediterranean dietary patterns

A Mediterranean diet primarily refers to a plant-based diet first described in the 1960s (136). General features include high consumption of fruits, vegetables, legumes, nuts, seeds, cereals and whole grains; moderate-to-high consumption of olive oil (as the principal source of fat); low-to-moderate consumption of dairy products, fish and poultry; low consumption of red meat; and low-to-moderate consumption of wine, mainly during meals (136,137). Systematic reviews and meta-analyses of randomized controlled feeding trials have shown that a Mediterranean-style dietary pattern improves glycemic control (50,138), and improves systolic BP, TC, HDL-C, TC:HDL-C ratio and TG in type 2 diabetes (139,140).

A low-CHO Mediterranean-style diet reduced A1C, delayed the need for antihyperglycemic drug therapy and increased rates of diabetes remission compared with a low-fat diet in overweight individuals with newly diagnosed type 2 diabetes at 8 years (141). Compared with a diet based on the American Diabetes Association recommendations, both traditional and low-CHO Mediterranean-style diets were shown to decrease A1C and TG, whereas only the low-CHO Mediterranean-style diet improved LDL-C and HDL-C at 1 year in persons with overweight and type 2 diabetes (142).

The Prevencion con Dieta Mediterranea (PREDIMED) study, a Spanish multicentre randomized trial of the effect of a Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts compared with a low-fat American Heart Association (AHA) control diet, was stopped early due to significant benefit with reduction in major CV events in 7,447 participants at high CV risk (including 3,614 participants [49%] with type 2 diabetes) (143). Both types of Mediterranean diets were shown to reduce the incidence of major CV events by approximately 30% without any subgroup differences between participants with and without diabetes over a median follow up of 4.8 years (143) (see Cardiovascular Protection in People with Diabetes chapter, p. S162). Both the extra-virgin olive oil and mixed nuts arms of the PREDIMED trial also reduced risk of incident retinopathy. No effect on nephropathy was detected (144).

Vegetarian dietary patterns

Vegetarian dietary patterns include lacto-ovovegetarian, lacto-vegetarian, ovovegetarian and vegan dietary patterns. A low-fat, ad libitum vegan diet has been shown to be just as beneficial as

conventional American Diabetes Association dietary guidelines in promoting weight loss and improving fasting BG and lipids over 74 weeks in adults with type 2 diabetes and, when taking medication changes into account, the vegan diet improved glycemia and plasma lipids more than the conventional diet (145). On both diets, weekly or biweekly nutrition and cooking instruction was provided by a dietitian or cooking instructor (145). Similarly, a calorie-restricted vegetarian diet was shown to improve BMI and LDL-C more than a conventional diet in people with type 2 diabetes (139). While both diets were effective in reducing A1C, more participants on the vegetarian diet had a decrease in antihyperglycemic medications compared to those on the conventional diet (43% vs. 5%, respectively). Subsequent systematic reviews and meta-analyses of the available randomized controlled trials have shown that vegetarian and vegan dietary patterns resulted in clinically meaningful improvements in A1C and FBG in people with type 1 and type 2 diabetes over 4 to 74 weeks (146,147), as well as body weight (148) and blood lipids (149) in people with and without diabetes over 3 to 74 weeks. Although most of these effects have been seen on high-CHO, low-fat vegetarian and vegan dietary patterns, there is evidence from the Eco-Atkins trial that these apply equally to low-CHO vegetarian dietary patterns (130 g/day [26% energy] CHO, 31% energy protein and 43% energy fat) for up to 6 months in individuals with overweight but without diabetes (150,151). A systematic review and meta-analysis of prospective cohort and cross-sectional observational studies showed a protective association between vegetarian dietary patterns and incident fatal and nonfatal CHD (152).

DASH and low-sodium dietary patterns

Dietary approaches to reducing BP have focused on sodium reduction and the Dietary Approaches to Stop Hypertension (DASH) dietary pattern. Although advice to the general population over 1 year of age is to achieve a sodium intake that meets the adequate intake (AI) target of 1,000 to 1,500 mg/day (depending on age, sex, pregnancy and lactation) (153), there is recent concern from prospective cohort studies that low-sodium intakes may be associated with increased mortality in people with type 1 (154) and type 2 diabetes (155).

The DASH dietary pattern does not target sodium reduction but rather emphasizes vegetables, fruits and low-fat dairy products, and includes whole grains, poultry, fish and nuts. It contains smaller amounts of red and processed meat, sweets, sugar-containing beverages, total and saturated fat, and cholesterol, and larger amounts of potassium, calcium, magnesium, dietary fibre and protein than typical Western diets (156,157). The DASH dietary pattern has been shown to lower systolic and diastolic BP compared with a typical American diet matched for sodium intake in people with and without hypertension, inclusive of people with well-controlled diabetes (156,157). These improvements in BP have been shown to hold at high (3,220 mg), medium (2,300 mg), and low (1,495 mg) levels of matched sodium intake (157). In addition to BP-lowering benefit, a systematic review and meta-analysis of randomized controlled trials showed that a DASH dietary pattern lowered lipids, including LDL-C in people with and without hypertension, some of whom had metabolic syndrome or diabetes (158).

In the only randomized controlled trial done exclusively in people with type 2 diabetes, a DASH dietary pattern compared with control diet for a moderate sodium intake (2,400 mg) was shown to decrease systolic and diastolic BP, A1C, FPG, weight, waist circumference, LDL-C and C-reactive protein (CRP) and to increase HDL-C over 8 weeks (159,160). A systematic review and meta-analysis of prospective cohort studies that included people with diabetes showed that adherence to a DASH dietary pattern was associated with a reduction in incident CVD (161).

Portfolio dietary pattern

The Portfolio Diet was conceived as a dietary portfolio of cholesterol-lowering foods, each with Federal Drug Administration (FDA) and/or Health Canada-approved health claims for cholesterol lowering or CV risk reduction. The 4 pillars of the Portfolio Diet include 2 g/day plant sterols (plant-sterol-containing margarines, supplements), 20 g/day viscous soluble fibres (gel-forming fibres from oats, barley, psyllium, konjac mannan, legumes, temperate climate fruits, eggplant, okra, etc.), 45 g/day plant protein (soy and pulses) and 45 g/day nuts (peanuts and tree nuts). Added to a low saturated fat NCEP Step II diet (≤7% saturated fat, ≤200 mg cholesterol), which reduces cholesterol by 5% to 10%, each component of the Portfolio Diet provides an additional 5% to 10% of LDL-C lowering. These small effects combine to provide a meaningful overall reduction in LDL-C lowering. The Portfolio Diet under conditions where all foods were provided has been shown to reduce LDL-C (~30%), hs-CRP (~30%) and calculated 10-year CVD risk by the Framingham Risk Score (~25%) in participants with hypercholesterolemia over 4 weeks (162). The reductions fell to 10% to 15% for LDL-C and 11% for 10-year CVD risk by the Framingham Risk Score (with greater effects in those who were more adherent) in a multicentre Canadian randomized controlled trial of effectiveness in which the Portfolio Diet was administered as dietary advice in participants with hypercholesterolemia over 6 months (163).

Although the Portfolio dietary pattern has not been formally tested in people with diabetes, each component has been shown individually to lower LDL-C in systematic reviews and meta-analyses of randomized controlled trials inclusive of people with diabetes (57,59–61,164–167). The results of the Combined Portfolio Diet and Exercise Study (PortfolioEx trial), a 3-year multicentre randomized controlled trial of the effect of the Portfolio Diet plus exercise on atherosclerosis, assessed by magnetic resonance imaging (MRI) in high CV risk people (ClinicalTrials.gov Identifier, NCT02481466), will provide important new data in people with diabetes, as approximately one-half of the participants will have type 2 diabetes.

Nordic dietary patterns

The Nordic Diet was developed as a Nordic translation of the Mediterranean, Portfolio, DASH and NCEP dietary patterns, using foods typically consumed as part of a traditional Nordic diet in the context of Nordic Nutrition Recommendations (168). It emphasizes ≥25% energy as whole-grain products, ≥175 g/day temperate fruits (apples and pears), ≥150 to 200 g/day berries (lingonberries and blueberry jam), ≥175 g/day vegetables, legumes (beans, peas, chickpeas and lentils), canola oil, ≥3 servings/week fatty fish (salmon, herring and mackerel), ≥2 servings/day low-fat dairy products, as well as several of the LDL-C-lowering foods common to the Portfolio Diet, including nuts (almonds), viscous fibres (oats, barley, psyllium), and vegetable protein (soy). The Nordic Diet has not been studied in people with diabetes; however, 3 high-quality randomized controlled trials have studied the effect of a Nordic Diet on glycemic control and other relevant cardiometabolic outcomes in people with central obesity or metabolic syndrome. These have shown improvements in body weight, insulin resistance, and lipids, including the therapeutically relevant LDL-C and non-HDL-C (169–171).

Popular weight-loss diets

Numerous popular weight-loss diets providing a range of macronutrient profiles are available to people with diabetes. Several of these diets, including the Atkins™, Zone™, Ornish™, Weight Watchers™ and Protein Power Lifeplan™ diets, have been subjected to investigation in longer-term, randomized controlled

trials in participants with overweight or obesity that included some people with diabetes, although no available trials have been conducted exclusively in people with diabetes. A systematic review and meta-analysis of 4 trials of the Atkins™ diet and 1 trial of the Protein Power Lifeplan™ diet (a diet with a similar extreme CHO restriction) showed that these diets were no more effective than conventional energy-restricted, low-fat diets in inducing weight loss with improvements in TG and HDL-C offset by increases in TC and LDL-C for up to 1 year (172). The Protein Power Lifeplan™ diet, however, did show improved A1C compared with an energy-reduced, low-fat diet at 1 year in the subgroup with type 2 diabetes (173). The Dietary Intervention Randomized Controlled Trial (DIRECT) showed that the Atkins™ diet produced weight loss and improvements in the lipid profile compared with a calorie-restricted, low-fat conventional diet; however, its effects were not different from that of a calorie-restricted Mediterranean-style diet at 2 years (174). Furthermore, the Mediterranean-style diet had a more favourable effect on FPG at 2 years in the subgroup of participants with type 2 diabetes (174). Another trial comparing the Atkins™, Ornish™, Weight Watchers™ and Zone™ diets showed similar weight loss and improvements in the LDL-C:HDL-C ratio without effects on FPG at 1 year in participants with overweight or obesity, of whom 28% had diabetes (175). A network systematic review and meta-analysis comparing all available trials of popular diets that were ≥3 months found that weight loss differences between individual diets was minimal at 12 months in individuals with overweight or obesity with a range of metabolic phenotypes, including type 2 diabetes (36).

Diets Emphasizing Specific Foods

Dietary pulses and legumes

Dietary pulses, the dried seeds of nonoil seed legumes, include beans, peas, chickpeas, and lentils. This taxonomy does not include the oil-seed legumes (soy, peanuts) or fresh legumes (peas, beans). Systematic reviews and meta-analyses of randomized controlled trials found that diets high in dietary pulses, either alone or as part of low-GI or high-fibre diets, lowered fasting BG and/or glycated blood proteins, including A1C (176) and improved LDL-C, BP and body weight in people with and without diabetes (177–179). In people with type 2 diabetes, a small randomized crossover trial not captured in the census of these meta-analyses, found that substituting pulse-based foods for red meat (average increase of 5 servings/week of pulses vs. a decrease of 7 servings/week red meat) in the context of a NCEP diet resulted in reductions in FBG, fasting insulin, TG and LDL-C without significant change in body weight (180). A systematic review and meta-analysis of prospective cohort studies, inclusive of people with diabetes, showed that the intake of 4 weekly 100 g servings of legumes is associated with decreased incident total CHD (181).

Fruit and vegetables

Eating Well with Canada's Food Guide recommends up to 7 to 10 servings of fruit and vegetables per day (182). Individual randomized controlled trials have shown that supplementation with fresh or freeze dried fruits improves A1C over 6 to 8 weeks in individuals with type 2 diabetes (183,184). A novel and simple technique of encouraging intake of vegetables first and other CHOs last at each meal was successful in achieving better glycemic control (A1C) than an exchange-based meal plan after 24 months of follow up in people with type 2 diabetes (185). A systematic review and meta-analysis of randomized controlled trials also showed that fruit and vegetables (provided as either foods or supplements) improved diastolic BP over 6 weeks to 6 months in individuals with the metabolic syndrome, some of whom had prediabetes (186). In people with type 1 and type 2 diabetes, an intervention to increase the intake of fruit, vegetables and dairy that only succeeded in increasing the intake of fruits and vegetables, led to a similar improvement in diastolic blood pressure and to a clinically meaningful regression in carotid intima medial thickness over 1 year (187). Systematic reviews and meta-analyses of prospective cohort studies inclusive of people with diabetes have shown that higher intakes of fruit and vegetables (>5 servings/day), fruit alone (>3 servings/day) or vegetables alone (>4 servings/day) is associated with a decreased risk of CV and all-cause mortality (79). Although there is a need to understand better the advantages of different fruit and vegetables in people with diabetes, higher intake of total fruit and vegetables remains an important part of all healthy dietary patterns.

Nuts

Nuts include both peanuts (a legume) and tree nuts, such as almonds, walnuts, pistachios, pecans, Brazil nuts, cashews, hazelnuts, macadamia nuts and pine nuts. A systematic review and meta-analysis of 12 randomized controlled trials of at least 3 weeks duration found that diets enriched with nuts at a median dose of 56 g/day resulted in a small yet significant reduction in A1C and FPG in people with diabetes (188). Another systematic review and meta-analysis of 49 randomized controlled trials of the effect of nuts on metabolic syndrome criteria found that diets emphasizing nuts at a median dose of ~50 g/day decreased FPG and TG over a median follow up of 8 weeks in people with and without diabetes (189). An individual patient-level meta-analysis of 25 nut intervention trials of the effect of nuts on lipid outcomes in people with normolipidemia or hypercholesterolemia (including 1 trial in people with type 2 diabetes) also showed a dose-dependent reduction in blood lipids, including the established therapeutic target LDL-C (190).

The PREDIMED trial showed that the provision of mixed nuts (30 g/day) added to a Mediterranean diet compared with a low-fat control diet decreased major CV events by 30% over a median follow up of 4.8 years in high-CV risk participants, half of whom had type 2 diabetes (143). A systematic review and meta-analysis of prospective cohort studies in people with and without diabetes also showed that the intake of 4 weekly 28.4 g servings of nuts was associated with comparable reductions in fatal and nonfatal CHD (181).

Despite concerns that the high energy density of nuts may contribute to weight gain, systematic reviews of randomized controlled trials have failed to show an adverse effect of nuts on body weight and measures of adiposity when nuts are consumed as part of balanced, healthy dietary patterns (189,191).

Whole grains

Health Canada defines whole grains as those that contain all 3 parts of the grain kernel (bran, endosperm, germ) in the same relative proportions as they exist in the intact kernel. Health Canada recommends that at least half of all daily grain servings are consumed from whole grains (192). Sources of whole grains include both the cereal grains (e.g. wheat, rice, oats, barley, corn, wild rice, and rye) and pseudocereal grains (e.g. quinoa, amaranth and buckwheat) but not oil seeds (e.g. soy, flax, sesame seeds, poppy seeds). Systematic reviews and meta-analyses of randomized controlled trials have shown that whole grain interventions, specifically with whole grain sources containing the viscous soluble fibre beta-glucan, such as oats and barley, improve lipids, including TG and LDL-C, in people with and without diabetes over 2 to 16 weeks of follow up (193). Whole grains have also been shown to improve glycemic control. Whole grains from barley have shown improvements in fasting glucose in people with and without diabetes (57)

and whole grains from oats have shown improvements in A1C and FPG in the subgroup with type 2 diabetes (194). In contrast, these advantages have not been seen for whole grain sources from whole wheat or wheat bran in people with type 2 diabetes (56,66,67). Systematic reviews and meta-analyses of prospective cohort studies have shown a protective association of total whole grains (where wheat is the dominant source) and total cereal fibre (as a proxy of whole grains) with incident CHD in people with and without diabetes (69,99). Although higher intake of all whole grains remains advisable (especially from oats and barley), more research is needed to understand the role of different sources of whole grains in people with diabetes.

Dairy products

Dairy products broadly include low- and full-fat milk, cheese, yogurt, other fermented products and ice cream. Evidence for the benefit of specific dairy products as singular interventions in the management of diabetes is inconclusive.

Systematic reviews and meta-analyses of randomized controlled trials of the effect of diets rich in either low- or full-fat dairy products have not shown any clear advantages for body weight, body fat, waist circumference, FPG or BP across individuals with different metabolic phenotypes (otherwise healthy, with overweight or obesity, or metabolic syndrome) (195,196). The comparator, however, may be an important consideration. Individual randomized controlled trials, which have assessed the effect of dairy products in isocaloric substitution with SSBs and foods, have shown advantages for visceral adipose tissue, systolic blood pressure and triglycerides in individuals with overweight or obesity over 6 months (197) and markers of insulin resistance in people with prediabetes over 6 weeks (198).

Other evidence from observational studies is suggestive of a weight loss and CV benefit. Large pooled analyses of the Harvard cohorts have shown that higher intakes of yogurt are associated with decreased body weight over 12 to 20 years of follow up in people with and without diabetes (98). Systematic reviews and meta-analyses of prospective cohort studies inclusive of people with diabetes have also shown a protective association of cheese with incident CHD; low-fat dairy products with incident CHD; and total, low-fat, and full-fat dairy products, and total milk with incident stroke over 5 to 26 years of follow up (199,200).

Special Considerations for People with Type 1 Diabetes and Type 2 Diabetes on Insulin

For persons on insulin, consistency in CHO intake (201) and spacing and regularity in meal consumption may help control BG levels (201–203). Inclusion of snacks as part of a person's meal plan should be individualized based on meal spacing, metabolic control, treatment regimen and risk of hypoglycemia, and should be balanced against the potential risk of weight gain (204,205).

The nutritional recommendations that reduce CV risk apply to both type 1 and type 2 diabetes. Studies have shown that people with type 1 diabetes tend to consume diets that are low in fibre, and high in protein and saturated fat (206). In addition, it was shown in the Diabetes Control and Complications Trial (DCCT), intensively treated individuals with type 1 diabetes showed worse diabetes control with diets high in total and saturated fat and low in CHO (207). Meals high in fat and protein may require additional insulin and, for those using CSII, the delivery of insulin may be best given over several hours (208). Algorithms for improved bolusing are under investigation. Heavy CHO loads (greater than 60 g) have been shown to result in greater glucose area under the curve and some risk of late postprandial hypoglycemia (209).

People with type 1 diabetes or type 2 diabetes requiring insulin, using a basal-bolus regimen, should adjust their insulin based on the CHO content of their meals, and inject their insulin within 15 minutes of eating with rapid-acting insulin analogues (208) and just prior to and if required up to 20 minutes after eating with faster-acting insulin aspart for optimal match between rapid insulin and glycemic meal rise (210) (see Glycemic Management of Type 1 Diabetes in Adults chapter, p. S80).

Intensive insulin therapy regimens that include multiple injections of rapid-acting insulin matched to CHO allow for flexibility in meal size and frequency (211,212). Improvements in A1C, BG and quality of life, as well as less requirement for insulin, can be achieved when individuals with type 1 diabetes (213) or type 2 diabetes (214) receive education on matching insulin to CHO content (e.g. CHO counting) (215,216). In doing so, dietary fibre and sugar alcohol should be subtracted from total CHO.

New interactive technologies, using mobile phones to provide information, CHO/insulin bolus calculations and telemedicine communications with care providers, have been shown to decrease both weight gain and the time required for education. They also improved individual quality of life and treatment satisfaction (217). Caution should be exercised in selection of smartphone bolus calculator apps for insulin calculation as there is a lack of regulation and surveillance, which may pose life-threatening risk and/or suboptimal control (218).

Other Considerations

Non-nutritive sweeteners

Sugar substitutes, which include high-intensity sweeteners and sugar alcohols, are regulated as food additives in Canada. Health Canada has approved the following high-intensity non-nutritive sweeteners for use in foods and chewing gum and/or as a tabletop sweetener: acesulfame potassium, aspartame, cyclamate, neotame, saccharin, steviol glycosides, sucralose, thaumatin and Monk fruit extract (219). Health Canada has set acceptable daily intake (ADI) values, which are expressed on a body weight basis and are considered safe daily intake levels over a lifetime (Table 2). These levels are considered high and are rarely achieved. Most have been shown to be safe when used by people with diabetes (220–222); however, there are limited data on the newer sweeteners, such as neotame and thaumatin in people with diabetes. Although systematic reviews and meta-analyses of prospective cohort studies inclusive of people with diabetes have shown an adverse association of non-nutritive sweetened beverages with weight gain, CVD and stroke, it is well recognized that these data are at high risk of reverse causality (223,224). The evidence from systematic reviews and meta-analyses of randomized controlled trials, which give a better protection against bias, have shown a weight loss benefit when non-nutritive sweeteners are used to

Table 2
Acceptable daily intake of sweeteners

Sweetener	Acceptable daily intake (mg/kg body weight/day)
Acesulfame potassium	15
Aspartame	40
Cyclamate	11
Erythritol	1,000
Neotame	2
Saccharin	5
Sucralose	8.8
Tagatose	80
Thaumatin	0.9

displace excess calories from added sugars (especially from SSBs) in overweight children and adults without diabetes (225), a benefit that has been shown to be similar to that seen with other interventions intended to displace excess calories from added sugars, such as water (225).

Sugar alcohols approved for use in Canada include: erythritol, isomalt, lactitol, maltitol, mannitol, sorbitol, xylitol. There is no ADI for sugar alcohols (except for erythritol) as their use is considered self-limiting due to the potential for adverse gastrointestinal symptoms. They vary in the degree to which they are absorbed, and their conversion rate to glucose is slow, variable and usually minimal, and may have no significant effect on BG. Thus, matching rapid-acting insulin to the intake of sugar alcohols is not recommended (226). Although there are no long-term, randomized controlled trials of consumption of sugar alcohols by people with diabetes, consumption of up to 10 g/day by people with diabetes does not appear to result in adverse effects (227).

Meal replacements

Weight loss programs for people with diabetes may use partial meal replacement plans. Commercially available, portion-controlled, vitamin- and mineral-fortified meal replacement products usually replace 1 or 2 meals per day in these plans. Randomized controlled feeding trials have shown partial meal replacement plans result in comparable (228) or increased (229,230) weight loss compared with conventional reduced-calorie diets for up to 1 year with maintenance up to 86 weeks in people with type 2 diabetes and overweight. This weight loss results in greater improvements in glycemic control over 3 months to 34 weeks (230,231) and reductions in the need for antihyperglycemic medications up to 1 year without an increase in hypoglycemic or other adverse events (229–231). Meal replacements with differing macronutrient compositions designed for people with diabetes have shown no clear advantage, although studies are lacking (232,233).

Alcohol

The same precautions regarding alcohol consumption in the general population apply to people with diabetes (234). Alcohol consumption should be limited to ≤2 standard drinks per day and <10 drinks per week for women and ≤3 standard drinks per day or <15 drinks per week for men (1 standard drink: 10 g alcohol, 341 mL 5% alcohol beer, 43 ml 40% alcohol spirits, 142 ml 12% alcohol wine) (235). Chronic heavy consumption (>21 standard drinks/week for men and >14 standard drinks/week for women) is associated with increased risk of CVD, microvascular complications and all-cause mortality in people with type 2 diabetes (236), while light-to-moderate intake shows an inverse association with A1C (237). For people with type 1 diabetes, moderate consumption of alcohol with, or 2 or 3 hours after, an evening meal may result in delayed hypoglycemia the next morning after breakfast or as late as 24 hours after alcohol consumption (238,239) and may impede cognitive performance during mild hypoglycemia (240). The same concern may apply to sulphonylurea- and insulin-treated individuals with type 2 diabetes (241). Health-care professionals should discuss alcohol use with people with diabetes (242) to inform them of the potential weight gain and risks of hypoglycemia (241).

Vitamin and mineral supplements

People with diabetes should be encouraged to meet their nutritional needs by consuming a well-balanced diet by following *Eating Well with Canada's Food Guide* (182). Routine vitamin and mineral supplementation is generally not recommended. Supplementation with 10 µg (400 IU) vitamin D is recommended for people >50 years of age (182). Supplementation with folic acid (0.4 to 1.0 mg) is recommended for women who could become pregnant (182). The need for further vitamin and mineral supplements should be assessed on an individual basis. As vitamin and mineral supplements are regulated as natural health products (NHP) in Canada, the evidence for their therapeutic role in diabetes has been reviewed in the Complementary and Alternative Medicine for Diabetes chapter, p. S154.

Fasting and diabetes

Within the lay literature, intermittent energy restriction strategies for weight loss have become more prevalent. To date, there is limited evidence for these approaches with people with type 2 diabetes. In 1 preliminary study comparing continuous energy restriction (5,000–6,500 kJ/day) to 2 days of severe energy restriction (1,670–2,500 kJ/day) each week (the so called 5:2 approach) over a 12-week period, the 5:2 program, while as effective as continuous energy restriction for weight loss and glycemic control, required careful medication adjustment to protect against the risk of hypoglycemia on severe energy restriction days (243).

Ramadan

Traditionally, Muslims with type 1 and insulin-requiring type 2 diabetes have been exempted from participation in Ramadan fasting, due to concerns of hypo- and hyperglycemia. Similarly, people on non-insulin antihyperglycemic agents associated with hypoglycemia are also considered high risk for fasting. People with diabetes who wish to participate in Ramadan fasting are encouraged to consult with their diabetes health-care team 1 to 2 months prior to the start of Ramadan.

While evidence for the impact of Ramadan fasting in individuals with type 1 diabetes is limited, the literature suggests that in people with well-controlled type 1 diabetes, complications from fasting are rare. A reduction in the total daily dose of insulin can reduce the incidence of hypoglycemia. CSII therapy or the use of multiple daily injections with rapid-acting insulin taken with meals and basal insulin, combined with frequent self-monitoring of blood glucose (SMBG) can help reduce the risk of hypo- and hyperglycemia. Individuals with a history of severe hypoglycemia or hypoglycemia unawareness should be discouraged from participating in Ramadan fasting (210,244). More information on Diabetes and Ramadan management is available at http://www.daralliance.org/daralliance/wp-content/uploads/IDF-DAR-Practical-Guidelines_15-April-2016_low.pdf (210).

Food skills

While there is no universally agreed upon definition of food skills, it is generally thought that they are interdependent technical, mechanical, conceptual and perceptual skills that are necessary to safely select and plan, prepare, and store nutritious and culturally-acceptable meals and snacks (245–247). Several studies suggest that food preparation and cooking skills are declining globally (245,248,249). Over the past several decades, in Canada, there has been an increase in processed, pre-prepared and convenience foods being purchased and assembled rather than meals being prepared using whole, basic ingredients (250). To our knowledge, there are no studies that have investigated food skills in people with diabetes. Nevertheless, targeted interventions to improve the food skills of people living with diabetes are prudent given that food is central to managing glycemic control.

RECOMMENDATIONS

1. People with diabetes should receive nutrition counselling by a registered dietitian to lower A1C levels [Grade B, Level 2 (3), for those with type 2 diabetes; Grade D, Consensus, for type 1 diabetes] and to reduce hospitalization rates [Grade C, Level 3 (8)].

2. Nutrition education may be delivered in either a small group or one-on-one setting [Grade B, Level 2 (18)]. Group education should incorporate adult education principles, such as hands-on activities, problem solving, role playing and group discussions [Grade B, Level 2 (19)].

3. Individuals with diabetes should be encouraged to follow *Eating Well with Canada's Food Guide* (182) in order to meet their nutritional needs [Grade D, Consensus].

4. In people with overweight or obesity with diabetes, a nutritionally balanced, calorie-reduced diet should be followed to achieve and maintain a lower, healthier body weight [Grade A, Level 1A (29,30)].

5. An intensive healthy behaviour intervention program, combining dietary modification and increased physical activity, may be used to achieve weight loss, improve glycemic control and reduce CV risk [Grade A, Level 1A (30)].

6. In adults with diabetes, the macronutrient distribution as a percentage of total energy can range from 45% to 60% carbohydrate, 15% to 20% protein and 20% to 35% fat to allow for individualization of nutrition therapy based on preferences and treatment goals [Grade D, Consensus].

7. People with type 2 diabetes should maintain regularity in timing and spacing of meals to optimize glycemic control [Grade D, Level 4 (203)].

8. To reduce the risk of CVD, adults with diabetes should avoid trans fatty acids (TFA) [Grade D, Level 4 (104)] and consume less than 9% of total daily energy from saturated fatty acids (SFA) [Grade C, Level 2 (105)] replacing these fatty acids with polyunsaturated fatty acids (PUFA), particularly mixed n-3/n-6 sources [Grade C, Level 3 (105)], monounsaturated fatty acids (MUFA) from plant sources, whole grains [Grade D, Consensus (107)] or low-GI carbohydrates [Grade D, Consensus (108)].

9. Adults with diabetes may substitute added sugars (sucrose, high fructose corn syrup, fructose, glucose) for other carbohydrates as part of mixed meals up to a maximum of 10% of total daily energy intake, provided adequate control of BG, lipids and body weight is maintained [Grade C, Level 3 (74,77,78,82)].

10. Adults with type 1 and type 2 diabetes may aim to consume 30 to 50 g/day of dietary fibre with a third or more (10 to 20 g/day) coming from viscous soluble dietary fibre to improve glycemic control [Grade C, Level 3 (57)] and LDL-C [Grade C, Level 3 (54,57,59)], and reduce CV risk [Grade D, Level 4 (69)].

11. Adults with diabetes should select carbohydrate food sources with a low-GI to help optimize glycemic control [Grade B, Level 2 (46,47) for type 1 diabetes; Grade B, Level 2 (32,44) for type 2 diabetes], to improve LDL-C [Grade C, Level 3 (49)] and to decrease CV risk [Grade D, Level 4 (52)].

12. The following dietary patterns may be considered in people with type 2 diabetes, incorporating patient preferences, including:
    a. Mediterranean-style dietary pattern to reduce major CV events [Grade A, Level 1A (143)] and improve glycemic control [Grade B, Level 2 (50,139)].
    b. Vegan or vegetarian dietary pattern to improve glycemic control [Grade B, Level 2 (145,251)], body weight [Grade C, Level 3 (148)], and blood lipids, including LDL-C [Grade B, Level 2 (149)] and reduce myocardial infarction risk [Grade B, Level 2 (152)].
    c. DASH dietary pattern to improve glycemic control [Grade C, Level 2 (159)], BP [Grade D, Level 4 (156–159)], and LDL-C [Grade B, Level 2 (158,159)] and reduce major CV events [Grade B, Level 3 (161)].
    d. Dietary patterns emphasizing dietary pulses (e.g. beans, peas, chickpeas, lentils) to improve glycemic control [Grade B, Level 2 (176)], systolic BP [Grade C, Level 2 (178)] and body weight [Grade B, Level 2 (179)].
    e. Dietary patterns emphasizing fruit and vegetables to improve glycemic control [Grade B, Level 2 (183,184)] and reduce CV mortality [Grade C, Level 3 (79)].
    f. Dietary patterns emphasizing nuts to improve glycemic control [Grade B, Level 2 (188)], and LDL-C [Grade B, Level 2 (190)].

13. People with type 1 diabetes may be taught how to match insulin to carbohydrate quantity and quality [Grade C, Level 2 (213)] or they may maintain consistency in carbohydrate quantity and quality [Grade D, Consensus].

14. People with diabetes using insulin and/or insulin secretagogues should be educated about the risk of hypoglycemia resulting from alcohol [Grade C, Level 3 (239)], and should be advised on preventive actions, such as carbohydrate intake and/or insulin dose adjustments and increased BG monitoring [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *AI*, adequate intake; *AMDRs*, acceptable macronutrient distribution ranges; *BG*, blood glucose; *BP*, blood pressure; *CAD*, coronary artery disease; *CHD*, coronary heart disease; *CHO*, carbohydrate; *CKD*, chronic kidney disease; *CRP*, C-reactive protein; *CSII*, continuous subcutaneous insulin infusion; *CV*, cardiovascular, *CVD*, cardiovascular disease; *DASH*, Dietary Approaches to Stop Hypertension; *DRIs*, dietary reference intakes; *FBG*, fasting blood glucose; *FPG*, fasting plasma glucose; *GI*, glycemic index; *HDL-C*, high density lipoprotein cholesterol; *HFCS*, high fructose corn syrup; *IFI*, intensive lifestyle intervention; *LC-PUFA*, long-chain polyunsaturated fatty acid; *LDL-C*, low density lipoprotein cholesterol; *MUFA*, monounsaturated fatty acids; *NCEP*, National Cholesterol Education Program; *NHP*; natural health product; *NPH*, neutral protamine Hagedorn; *PUFA*, polyunsaturated fatty acids; *RDA*, recommended dietary allowance; *SMBG*, self-monitoring of blood glucose; *SSBs*, sugar-sweetened beverages; *TC*, total cholesterol; *TFA*, trans fatty acids; *TG*, triglycerides.

Other Relevant Guidelines

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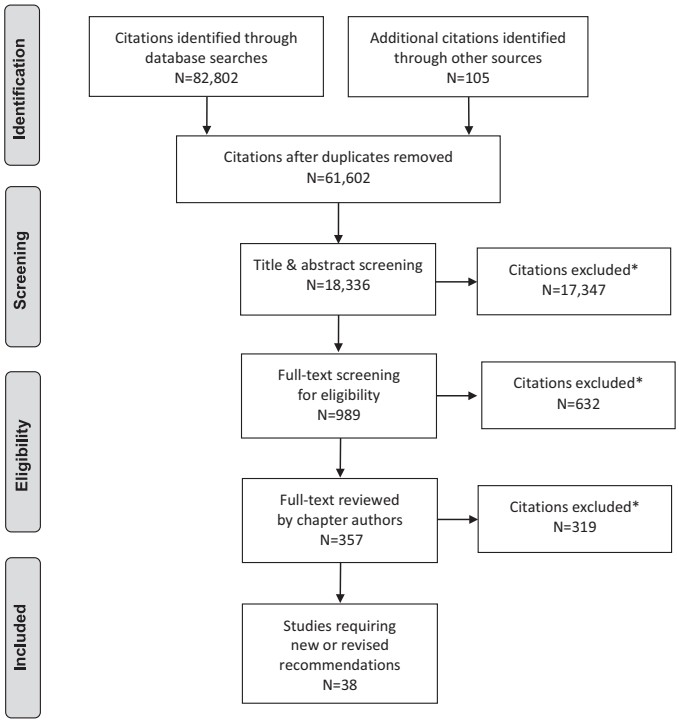
Literature Review Flow Diagram for Chapter 11: Nutrition Therapy



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Glycemic Management in Adults With Type 1 Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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This chapter is dedicated to Dr. Angela McGibbon who passed away from a sudden illness on February 11, 2018. She had an extraordinary dedication to diabetes care and a passion for teaching the importance of patient care and compassion. Her leadership and outstanding contributions to the diabetes community will always be remembered.

KEY MESSAGES

- Basal-bolus insulin therapies (i.e. multiple daily injections or continuous subcutaneous insulin infusion) are the preferred insulin management regimens for adults with type 1 diabetes.
- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.
- All individuals with type 1 diabetes should be counselled about the risk, prevention and treatment of hypoglycemia. Avoidance of nocturnal hypoglycemia may include changes in insulin therapy and increased monitoring.
- If glycemic targets are not met with optimized multiple daily injections, continuous subcutaneous insulin infusion may be considered. Successful continuous subcutaneous insulin infusion therapy requires appropriate candidate selection, ongoing support and frequent involvement with the health-care team.
- Continuous glucose monitoring may be offered to people not meeting their glycemic targets, who will wear the devices the majority of the time, in order to improve glycemic control.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Insulin therapy is required for the treatment of type 1 diabetes.
- There are a variety of insulins and methods of giving insulin to help manage type 1 diabetes.
- Insulin is injected by pen, syringe or insulin pump.
- Your health-care provider will work with you to determine such things as:
  - The number of insulin injections you need per day
  - The timing of your insulin injections
  - The dose of insulin you need with each injection
  - If and when an insulin pump is appropriate for you
  - Your pump settings if you are giving insulin that way.
- The insulin treatment your health-care provider prescribes will depend on your goals, lifestyle, meal plan, age and general health. Social and financial factors may also be taken into account.
- Learning to avoid and treat hypoglycemia (low blood glucose) is an important part of your education. The ideal balance is to achieve blood glucose levels that are as close to target as possible while avoiding hypoglycemia.

Introduction

Insulin is lifesaving pharmacological therapy for people with type 1 diabetes. Insulin preparations are primarily produced by recombinant DNA technology and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues) to alter pharmacokinetics. Human insulin and insulin analogues are preferred and used by most adults with type 1 diabetes; however, preparations of animal-sourced insulin are still accessible in Canada (1) although rarely required. Inhaled insulin is currently not approved for use in Canada.

Insulin preparations are classified according to their duration of action and are further differentiated by their time of onset and peak actions (see Appendix 6. Types of Insulin). For most adults with type 1 diabetes, premixed insulin preparations are not suitable as frequent adjustments of insulin are required. Insulin delivered by basal-bolus injection therapy or continuous subcutaneous insulin infusion (CSII, also called insulin pump therapy) as basal and bolus regimens are preferred. Avoidance of hypoglycemia with all regimens is a priority.

Achieving optimal glycemic targets, while avoiding hypoglycemia, can be challenging and requires individualized insulin regimens, which may include specialized insulin delivery devices and glucose monitoring often introduced in an escalating manner, starting with basal-bolus injection therapy then, in some cases, moving to CSII either with or without sensor augmentation. Continuous glucose monitoring (CGM) may be used with basal-bolus injection therapy or CSII. The role of adjuvant (noninsulin) injectable or oral antihyperglycemic medications in glycemic control is limited for most people with type 1 diabetes. Noninsulin pharmacotherapy for prevention of complications and treatment of risk factors is addressed in other chapters (see Cardiovascular Protection in People with Diabetes chapter, p. S162; Chronic Kidney Disease in Diabetes chapter, p. S201). Hypoglycemia as it relates to insulin therapy in type 1 diabetes is discussed here, and hypoglycemia in general is addressed in the Hypoglycemia chapter, p. S104.

Conflict of interest statements can be found on page S84.

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Insulin Therapy with Basal-Bolus Injection Therapy

People with type 1 diabetes are initiated on insulin therapy immediately at diagnosis. This requires both the selection of an insulin regimen and comprehensive diabetes education. Insulin regimens, usually with basal and bolus insulins, should be tailored to the individual's age, general health, treatment goals, lifestyle, diet, hypoglycemia awareness status, ability for self-management and adherence to treatment. Social and financial aspects also should be considered. After insulin initiation, some individuals experience a "honeymoon period," during which insulin requirements may be lower than expected; however, this period is transient (usually weeks to months), and insulin requirements typically increase and stabilize with time.

The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular and cardiovascular (CV) complications (2,3). The most successful management in the majority of adults with type 1 diabetes is based on basal-bolus injection therapy or CSII. Such regimens attempt to replicate normal pancreatic secretion of insulin.

Currently, new concentrated insulin preparations are available in basal and bolus formats. Sometimes they have identical pharmacokinetic and pharmacodynamic properties to the original preparation and other concentrated insulins have different pharmacological properties (see Appendix 6. Types of Insulin). These are further described below in the basal and bolus sections. In addition, biosimilar basal insulin is also available.

Basal insulin and basal-bolus injection therapy

Basal insulin refers to long- or intermediate-acting insulin, which provides control of glucose in the fasting state and between meals. Basal insulin is given once or twice a day and includes long-acting insulin analogues and intermediate-acting insulin neutral protamine Hagedorn (NPH). Insulin onset, peak and duration are shown in Appendix 6. Types of Insulin. Detemir insulin is available as a 100 units/mL formulation (U-100) (Levemir®). Glargine insulin is available as a 100 units/mL formulation (U-100) (Lantus™), a 300 units/mL formulation (U-300) (Toujeo®) and as a 100 units/mL biosimilar product (U-100) (Basaglar®). Degludec insulin is available as a 100 units/mL (U-100) and 200 units/mL (U-200) formulation (Tresiba®).

When used as a basal insulin in type 1 diabetes, the U-100 long-acting analogues, insulin detemir and insulin glargine (with rapid-acting insulin analogues for meals) resulted in lower fasting plasma glucose (FPG) levels and less hypoglycemia (4–7) or nocturnal hypoglycemia compared with once- or twice-daily NPH insulin (4,6–11). Given the potential severe consequences of nocturnal hypoglycemia, the avoidance of this complication is of great clinical importance.

Biosimilar insulin glargine has the identical amino acid sequence as glargine and is produced through a different manufacturing process. Biosimilar insulin glargine has been shown to have similar efficacy and safety outcomes in adults with type 1 diabetes maintained or switched from U-100 glargine (12).

Insulin glargine U-300 is a concentrated basal insulin, which appears to have a consistent, gradual and extended flat release from subcutaneous tissue with a longer duration of action (>30 hours) than U-100 glargine (13,14). Insulin glargine U-300 has been compared to insulin glargine U-100 in adults with type 1 diabetes and found to produce similar changes in A1C and similar or lower risk of hypoglycemia (13,15). Confirmed or severe nocturnal hypoglycemia was significantly lower in 1 study (16) but not in other shorter trials (15). Insulin glargine U-300 may require a higher dose than insulin glargine U-100 and may result in less weight gain (15,17).

Insulin degludec is a basal insulin with a long duration of action (42 hours) (14,18,19) in a once-daily injection that provides a consistent, flat glucose-lowering profile with low day-to-day variability (18,19). It provides similar glycemic control, but with less nocturnal hypoglycemia (20) and reduced basal and total insulin dose when compared to insulin glargine (21–23) and insulin detemir (24,25). The prolonged duration of action of insulin degludec allows for flexible timing of dosing without compromising metabolic control or safety (26). The 2 formulations of insulin degludec (U-100 and U-200) have similar glucose-lowering effects and half-lives (14).

Bolus insulin and basal-bolus injection therapy

Bolus insulin refers to rapid- or short-acting insulin given to control the glycemic rise at meals and to correct hyperglycemia. The prandial injection dose is decided based on carbohydrate content, carbohydrate-to-insulin ratio for each meal, planned exercise, time since last insulin dose and blood glucose level. Bolus insulins include rapid-acting insulin analogues (insulin aspart, insulin faster-acting aspart, insulin glargine, insulin lispro) and short-acting insulin (regular insulin).

Preprandial injections of rapid-acting insulin analogues result in a lower postprandial glucose and improved overall glycemic control (27–30). Insulin aspart, glulisine and lispro should be administered 0 to 15 minutes before the start of the meal while short-acting regular insulin should be administered 30 to 45 minutes before the start of the meal. Faster-acting insulin aspart may be administered at the start of the meal or, when necessary, up to 20 minutes after the start of the meal (31). When required, insulin aspart, glulisine and lispro can be administered from 0 to 15 minutes after the start of a meal although better control of postprandial hyperglycemia is seen with preprandial injections.

Insulin aspart and lispro have been associated with reduced nocturnal hypoglycemia, slightly lower A1C, improved postprandial glucose (30,32) and improved quality of life (33) when compared to short-acting insulin. Insulin glulisine has been shown to be equivalent to insulin lispro for glycemic control, with most effective A1C reduction when given before meals (27,34). Faster-acting insulin aspart has an earlier onset than insulin aspart (see Appendix 6. Types of Insulin). In type 1 diabetes, faster-acting insulin aspart demonstrated noninferiority with respect to A1C reduction and superior postprandial glucose control vs. insulin aspart (31).

Hypoglycemia and Insulin Therapy

Hypoglycemia is the most common adverse effect of insulin therapy in people with type 1 diabetes (for definitions see Hypoglycemia chapter, p. S104). In the DCCT, 35% of participants in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (2,35,36). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated people with type 1 diabetes, respectively (37). With adequate self-management education, appropriate glycemic targets, self-monitoring of blood glucose and support, intensive therapy may result in less hypoglycemia than reported in the DCCT (38–41), particularly with modern insulin formulations.

The frequency of hypoglycemic events is reduced with rapid-acting insulin analogues compared with regular insulin (8,42–44) although there are no differences in the magnitude and temporal pattern of the physiological, symptomatic and counterregulatory hormonal responses to hypoglycemia induced by regular human insulin or rapid-acting analogues (45,46).

Long-acting insulin analogues reduce the incidence of hypoglycemia and nocturnal hypoglycemia when compared to

intermediate-acting insulin as the basal insulin (10,47–51). Lifestyle factors and changes from usual self-management behaviours (e.g. eating less food, taking more insulin, increased physical activity) account for 85% of hypoglycemic episodes (52,53). Adding bedtime snacks may be helpful to prevent nocturnal hypoglycemia among those taking NPH as the basal insulin or in those individuals at high risk of severe hypoglycemia (regardless of insulin type), particularly when bedtime plasma glucose (PG) levels are <7.0 mmol/L (54,55).

Knowledge of the acute effects of exercise is essential. Low- to moderate-intensity exercise lowers BG levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin, and the type and timing of physical activity. In contrast, high-intensity exercise raises BG levels during and immediately after the event but may result in hypoglycemia hours later. SMBG before, during and after exercise is important for establishing response to exercise and guiding the appropriate management of exercise. If ketosis is present, exercise should not be performed as metabolic deterioration can occur (56) (see Physical Activity and Diabetes chapter, p. S54).

Hypoglycemia prevention and treatment is discussed in more detail in the Hypoglycemia chapter, p. S104; however, it is the limiting factor in most treatment strategies for type 1 diabetes. Increased education, monitoring of blood glucose, changing insulins and insulin routines, and the use of new diabetes technologies may be required (57,58). An educational program for people with impaired hypoglycemia awareness in which participants were randomized to either CSII or basal-bolus injection therapy and to either SMBG or real-time CGM showed that severe hypoglycemia and hypoglycemia awareness were improved to a similar degree regardless of the insulin delivery method or monitoring method used, although treatment satisfaction was higher with CSII compared with basal-bolus injection therapy (59).

Continuous Subcutaneous Insulin Infusion Therapy

CSII or insulin pump therapy is a safe and effective method of intensive insulin delivery in type 1 diabetes. Both CSII and basal-bolus injection therapy are considered the standard of care for adults with type 1 diabetes. While many people with type 1 diabetes are on CSII due to personal preference, there are some medical indications for CSII therapy. In particular, CSII can be considered in people with type 1 diabetes who do not reach glycemic targets despite optimized basal-bolus injection therapy, as well as in the following individuals: those with significant glucose variability; frequent severe hypoglycemia and/or hypoglycemia unawareness; significant "dawn phenomenon" with rise of blood glucose early in the morning; very low insulin requirements; adequate glycemic control but suboptimal treatment satisfaction and quality of life or women contemplating pregnancy (60–63).

It is important to select the appropriate individual for pump therapy. Appropriate candidates should be motivated individuals, currently on optimized basal-bolus injection therapy, who are willing to frequently monitor BG, understand sick-day management and attend follow-up visits as required by the health-care team (62,63). The health-care team should ideally be interprofessional and include a diabetes educator and a physician/nurse practitioner with special interest and expertise in CSII therapy. Comprehensive preparation, initiation and follow up should be provided by the team and are critical for the success of CSII. The health-care team should periodically re-evaluate whether continued pump therapy is appropriate for the individual (62).

Rapid-acting insulin analogues have replaced short-acting insulin in CSII therapy for several reasons, including their demonstrated safety, efficacy and more physiologic and rapid action (64). Although not recommended in Canada, insulin Humulin R® is still indicated for use in CSII while insulin Novolin Toronto® is not. The 3 rapid-acting insulin analogues approved for CSII are insulin lispro, aspart and glulisine. Faster-acting insulin aspart is not yet approved in Canada for use in CSII. Among people using CSII, insulin lispro has been demonstrated to provide similar (65) or superior (66,67) A1C lowering, overall improvement in postprandial hyperglycemia (66,67), and no increase in hypoglycemia (66,67) when compared to short-acting insulin. Insulin aspart provides a similar effect on A1C and hypoglycemia risk as short-acting insulin or lispro (65). Insulin glulisine has a similar effect on A1C when compared to aspart (68,69) and lispro (68); however, the rate of symptomatic hypoglycemia was higher with use of glulisine in 1 crossover study (68).

Clinical trial data on the rate of catheter occlusions among users of the 3 rapid-acting insulins do not show any consistent differences (68,69). In vitro studies have demonstrated some differences in product stability and catheter occlusions (64). Insulin glulisine is indicated to be changed at least every 48 hours in the infusion set and reservoir; aspart and lispro are to be changed according to the pump manufacturer's recommendations.

A1C benefit of CSII therapy

CSII treatment has gone through many advances since it was first introduced. Many studies using CSII have been limited by small numbers of participants, short duration and the inability to adequately blind participants. Interpretation of meta-analyses is difficult as some included trials with short-acting insulin in the CSII arm (70,71), and another included trials with only NPH-based basal-bolus injection therapy as the comparator (72). The most relevant meta-analyses included trials using rapid-acting insulin analogues in the CSII arms and NPH- or glargine-based basal-bolus injection therapy as the comparators (73–75). Trials using other basal analogues as the comparator were not identified. Use of CSII was shown to reduce A1C by 0.19% to 0.3% in adults (73,75) or in participants with a mean age over 10 years (74). An observational study of real-life outcomes using CSII therapy demonstrated that those who had a pre-CSII A1C of >9.0% had the greatest improvement in A1C after CSII initiation; people with a pre-CSII A1C of ≤7.0% were likely to maintain their A1C in the same range on CSII; and for all groups, A1C values slowly increased with time but remained below the pre-CSII levels (76).

A major advancement in CSII treatment has been the addition of continuous glucose monitoring systems (CGM) and sensor-augmented pumps (SAP) which is the use of CSII plus CGM. In people with type 1 diabetes with suboptimal control on basal-bolus injection therapy and SMBG, the introduction of CSII and CGM at the same time offers a more substantial A1C benefit over continuation of basal-bolus injection therapy with SMBG. In 2 major trials, participants suboptimally controlled on basal-bolus injection therapy were randomized to either continue basal-bolus injection therapy or to start SAP. One small trial in adults showed a mean difference in change in A1C of -1.21% in favour of the SAP arm (77), without an increase in hypoglycemia. In a larger trial of children and adults, end-of-trial mean difference in change in A1C was -0.6% in favour of the SAP arm, in all participants and in adults specifically (78) without an increase in hypoglycemia. Duration of sensor use was associated with the greatest decline in A1C in 1 trial (78) but not the other (77).

Further enhancement of sensor-augmented CSII technology has been the low glucose suspend function in which insulin delivery is stopped for a defined period of time if a critically low glucose threshold is detected on the CGM. To date, only 2 major trials have been published regarding this technology (79,80). Hypoglycemia benefit, rather than the change in A1C, was the primary focus of

these trials and no conclusions can be made about A1C benefit of SAP with low glucose suspend.

CSII and hypoglycemia

The benefit of CSII with regard to hypoglycemia has been difficult to evaluate given that many studies were of short duration, had small numbers and rates of severe hypoglycemia were generally low. Severe hypoglycemia has not been significantly different between users of CSII and basal-bolus injection therapy, based on meta-analyses which included only rapid-acting insulin analogues in the CSII arms (73–75). However, in a meta-analysis of trials of participants with a high baseline rate of severe hypoglycemia (>10 episodes per 100 patient-years while on basal-bolus injection therapy), the use of CSII was associated with a reduction of severe hypoglycemia (81) when compared to basal-bolus injection regimens using older nonanalogue basal insulins.

Nonsevere hypoglycemia has been inconsistently defined and reported but, overall, CSII does not appear to reduce the frequency of nonsevere hypoglycemia. No differences have been found between CSII and basal-bolus injection therapy for nocturnal hypoglycemia (75). No consistent conclusions could be drawn regarding nonsevere hypoglycemia in 2 meta-analyses (73,74). In 1 meta-analysis, minor hypoglycemia, calculated as the mean number of mild episodes per patient per week, was found to be nonsignificantly lower in users of CSII in crossover trials of adolescents and adults (75).

When CSII has been introduced together with CGM (SAP), A1C has been consistently lowered without increasing the rate of hypoglycemia (77,78). Time spent in hypoglycemia and severe hypoglycemia was not consistently different (77,78) but hypoglycemia fear improved more in adults randomized to SAP compared to those randomized to continuation of basal-bolus injection therapy (82).

One large randomized controlled trial in adults compared the use of SAP with and without the low glucose suspend feature (80). Participants were randomized if they had demonstrated nocturnal hypoglycemia and high sensor compliance during the run-in phase. SAP with low glucose suspend led to a reduction in nocturnal hypoglycemia with no increase in A1C or ketoacidosis (80). In another trial of adults and children with hypoglycemia unawareness, the use of SAP with low glucose suspend, compared to the use of CSII and SMBG, was shown to reduce the rate of moderate and severe hypoglycemia (79) although this outcome lost significance when outliers were excluded. Overall, the use of SAP with low glucose suspend is promising for nocturnal hypoglycemia and hypoglycemia unawareness but more studies are needed.

CSII and quality of life

Several studies have demonstrated improved quality of life (QOL) or improved treatment satisfaction (TS) with CSII therapy whether due to improved glycemic control, flexibility in insulin administration, patient selection and/or motivation. The various studies used different measurement tools or older insulin regimens (70). Compared with basal-bolus injection therapy plus SMBG, CSII plus SMBG has been associated with improved diabetes-specific QOL (73) and TS (70). When compared with basal-bolus injection therapy plus SMBG, CSII plus CGM (SAP) has been associated with improved diabetes-specific health-related QOL (82), diabetes-related distress (77), TS (77,82), perceived frequency of hyperglycemia (77), fear of hypoglycemia (82), and general health and social functioning (77). Compared with CSII plus SMBG, SAP has been associated with improved TS (83,84), lower perceived frequency of hypoglycemia (83), less worry about hypoglycemia (83), and better treatment convenience and flexibility (84).

Data regarding long-term diabetes complications, adverse events, cost and mortality among users of CSII have been limited (70). An observational study of a large population-based Swedish national diabetes registry revealed lower cardiovascular (CV) mortality in users of CSII compared with users of basal-bolus injection therapy (85).

Continuous Glucose Monitoring

Adults with type 1 diabetes derive an A1C benefit from CGM, when compared to SMBG, regardless of the baseline level of A1C or the type of intensive insulin therapy and delivery. CGM may be done in a blinded manner ("professional" CGM), so that results are not immediately visible to the person with diabetes, or more commonly, in "real-time" where people with diabetes can immediately see values and take action if necessary. The discussion here refers to the studies using "real-time" CGM. The recommendations and findings presented here are consistent with those of the Endocrine Society Clinical Practice Guideline on this topic, which recommended the use of real-time CGM for adult patients with either A1C above target or who are well-controlled (at A1C target), provided that the devices are worn nearly daily (63).

In people with diabetes with a baseline A1C >7.0%, the use of CGM compared to SMBG results in an A1C reduction of approximately 0.4% to 0.6%. This A1C change has been demonstrated in adults using CSII (86), adults and children using either basal-bolus injection therapy or CSII (87), adults and children using CSII (88,89) and adults using basal-bolus injection therapy (90,91). In contrast, two trials in adults and children using CSII showed no A1C difference between users of CGM and SMBG (92,93) except in those who wore the sensor at least 70% of the time in 1 of the studies (92). Even with a baseline A1C <7.0%, in adults and children using basal-bolus injection therapy or CSII, the A1C benefit of CGM has been -0.27 to -0.34% (94,95). Meta-analyses of trials regardless of the baseline A1C have estimated the overall between-group change from baseline A1C to be approximately -0.2% to -0.3% in favour of CGM (73,96,97), and in adults specifically the A1C benefit has been -0.38% (73). The greatest A1C benefit has been demonstrated with the greatest duration of sensor use (97,73) and with the highest A1C at baseline (97).

The A1C benefits of CGM do not appear to be associated with excess hypoglycemia. Time spent in hypoglycemia was either lower in the CGM group (88,90,93,95) or was not significantly different between groups (86,92,94). Severe hypoglycemia was uncommon in these studies, and 1 study showed an increase in severe hypoglycemia with CGM (93) but this was not consistent in other trials.

People with type 1 diabetes with an A1C <7.0% may find that the use of CGM allows them to maintain their A1C at target without more hypoglycemia. One trial in patients with an A1C <7.5% (mean A1C at randomization, 6.9%) demonstrated shorter time in hypoglycemia with reduction of A1C in the CGM group compared with the SMBG group (95). In another trial of subjects with an A1C <7% (mean baseline A1C 6.4%-6.5%), while time in hypoglycemia was not significantly reduced, combined A1C and hypoglycemia endpoints favoured the CGM group, including the reduction of A1C without a substantial increase of hypoglycemia, and the reduction of hypoglycemia without worsening of A1C by 0.3% or more (94).

When CGM is introduced together with CSII therapy (SAP), the A1C benefit has been larger when compared to maintenance of basal-bolus injection therapy plus SMBG, without an increase of hypoglycemia (73,77,78,96).

Among adults with impaired hypoglycemia awareness, CGM has been shown to reduce severe hypoglycemia and increase time in normoglycemia in 1 trial of participants with high compliance of sensor use (98). In contrast, in another trial using a standardized

education program, hypoglycemia awareness and severe hypoglycemia improved to a similar degree in participants randomized to CGM or SMBG, but sensor compliance was not high in this trial (59). This technology is, therefore, promising in this group but more studies are required.

Adjunctive Therapy for Glycemic Control

As the incidence of obesity and overweight increases in the population, including in those with type 1 diabetes, there is growing interest in the potential use of noninsulin antihyperglycemic agents that improve insulin sensitivity or work independently of insulin and may provide additional glucose-lowering benefits without increasing hypoglycemia risk (99,100). In several studies, the use of metformin in type 1 diabetes reduces insulin requirements and may lead to modest weight loss (101) without increased hypoglycemia. In the clinical trial setting, metformin does not result in improved A1C, fasting glucose or triglyceride (TG) levels (101) and changes do not persist long term (102).

Several small trials using SGLT2 inhibitors in type 1 diabetes demonstrated a reduction in mean glucose levels (103) and A1C (104,105). An increase in diabetic ketoacidosis (DKA) was also seen, which may be as high as 6% of participants in an 18-week study (105). DKA may have been precipitated by other factors, and several presented with glucose <13.9 mmol/L (106). A1C reduction and increased risk of ketosis was found when this class was added to insulin and liraglutide (107). Although early data are cautiously positive for the use of this class in type 1 diabetes, better understanding of the risk for euglycemic DKA is needed (99,100,108) and SGLT2 inhibitors do not have an indication for use in type 1 diabetes (see Hyperglycemic Emergencies in Adults chapter, p. S109).

GLP-1 receptor agonists have been studied as add-on therapy to insulin in type 1 diabetes (109–111). Addition of liraglutide allowed a reduction in insulin dose and weight (110,111) without consistent results on hypoglycemia risk or A1C reduction in normal weight (112) or overweight (113) people with type 1 diabetes. Liraglutide may be associated with hyperglycemia and ketosis with the 1.8 mg dose in some studies (110,111) but not others (109). There is no current indication for use of liraglutide in type 1 diabetes. Studies of other GLP-1 receptor agonists in type 1 diabetes have been limited (109).

RECOMMENDATIONS

1. In adults with type 1 diabetes, basal-bolus injection therapy or CSII as part of an intensive diabetes management regimen should be used to achieve glycemic targets [Grade A, Level 1A (2)].

2. In adults with type 1 diabetes using basal-bolus injection therapy or CSII, rapid-acting insulin analogues should be used in place of regular insulin to improve A1C and to minimize the risk of hypoglycemia [Grade B, Level 2 (30,32) for basal-bolus injection therapy; Grade B, Level 2 (66,67) for lispro in CSII; Grade B, Level 2 (65) for aspart in CSII; Grade D, Consensus, for glulisine in CSII] and to achieve postprandial BG targets [Grade B, Level 2 (32) for basal-bolus injection therapy; Grade B, Level 2 (66) for CSII].

3. In adults with type 1 diabetes on basal-bolus injection therapy:
   a. A long-acting insulin analogue may be used in place of NPH to reduce the risk of hypoglycemia [Grade B, Level 2 for detemir (7,50); Grade B, Level 2 for glargine U-100 (4,5,51); Grade D, Consensus for degludec and glargine U-300], including nocturnal hypoglycemia [Grade B, Level 2 (7) for detemir; Grade B, Level 2 (4) for glargine U-100; Grade D, Consensus for degludec, and glargine U-300].
   b. Degludec may be used instead of detemir or glargine U-100 to reduce nocturnal hypoglycemia [Grade B, Level 2 (24) compared to detemir; Grade C, Level 3 (20) compared to glargine U-100].

4. All individuals with type 1 diabetes and their support persons should be counselled about the risk and prevention of hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].

5. In adults with type 1 diabetes and hypoglycemia unawareness, the following nonpharmacological strategies may be used to reduce the risk of hypoglycemia:
   a. A standardized education program targeting rigorous avoidance of hypoglycemia while maintaining overall glycemic control [Grade A, Level 1A (59)]
   b. Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus]
   c. CGM with high sensor adherence in those using CSII [Grade C, Level 3 (98)]
   d. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade C, Level 3 (15,16)].

6. In adults with type 1 diabetes on basal-bolus injection therapy who are not achieving glycemic targets, CSII with or without CGM may be used to improve A1C [Grade B, Level 2 (77,78) with CGM; Grade B, Level 2 (73–75) without CGM].

7. In adults with type 1 diabetes,
   a. CSII may be used instead of basal-bolus injection therapy to improve treatment satisfaction [Grade C, Level 3 (70)]
   b. CSII plus CGM may be used instead of basal-bolus injection therapy or CSII with SMBG to improve quality of life, treatment satisfaction and other health-quality-related outcomes [Grade B, Level 2 (77,84)].

8. Adults with type 1 diabetes on CSII should undergo periodic evaluation to determine whether continued CSII is appropriate [Grade D, Consensus].

9. In adults with type 1 diabetes and an A1C at or above target, regardless of insulin delivery method used, CGM with high sensor adherence may be used to improve or maintain A1C [Grade B, Level 2 (97)] without increasing hypoglycemia [Grade C, Level 3 (97)].

10. In adults with type 1 diabetes experiencing nocturnal hypoglycemia and using CSII and CGM, SAP with low glucose suspend may be chosen over SAP alone to reduce nocturnal hypoglycemia [Grade B, Level 2 (80)].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *CGM*, continuous glucose monitoring; *CSII*, continuous subcutaneous insulin infusion; *DHC*, diabetes health care; *QOL*, quality of life; *RAIA*, rapid-acting insulin analogues; *SAP*, sensor augmented pump, *SMBG*, self-monitoring of blood glucose. *TS*, treatment satisfaction.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Monitoring Glycemic Control, p. S47
Physical Activity and Diabetes, p. S54
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Hypoglycemia, p. S104
In-Hospital Management of Diabetes, p. S115
Management of Acute Coronary Syndromes, p. S190
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255
Diabetes in Older People, p. S283

Relevant Appendix

Appendix 6. Types of Insulin

Author Disclosures

Dr. Adams reports personal fees from Novo Nordisk, Sanofi, Merck, AstraZeneca, Medtronic, Boehringer Ingelheim, Janssen, and Valeant,

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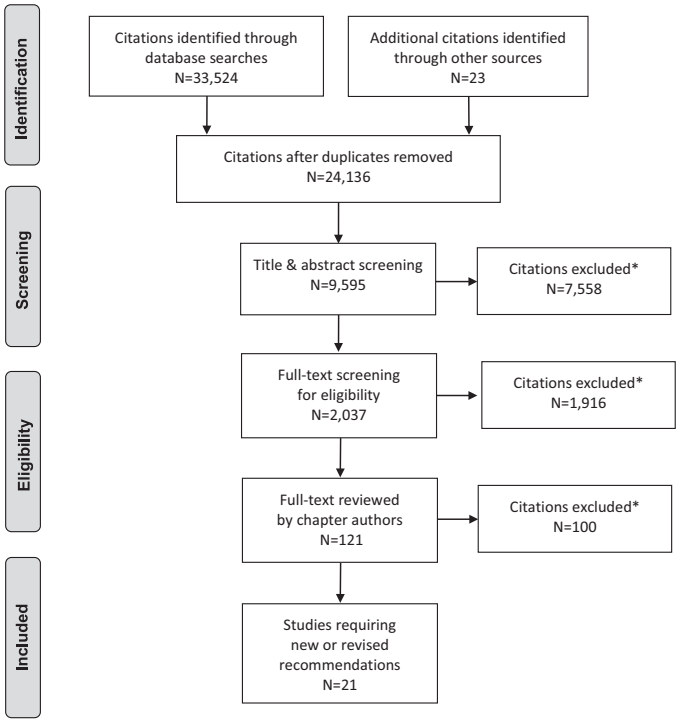
Literature Review Flow Diagram for Chapter 12: Glycemic Management in Adults with Type 1 Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Healthy behaviour interventions should be initiated in people newly diagnosed with type 2 diabetes.
- In people with type 2 diabetes with A1C <1.5% above the person's individualized target, antihyperglycemic pharmacotherapy should be added if glycemic targets are not achieved within 3 months of initiating healthy behaviour interventions.
- In people with type 2 diabetes with A1C ≥1.5% above target, antihyperglycemic agents should be initiated concomitantly with healthy behaviour interventions, and consideration could be given to initiating combination therapy with 2 agents.
- Insulin should be initiated immediately in individuals with metabolic decompensation and/or symptomatic hyperglycemia.
- In the absence of metabolic decompensation, metformin should be the initial agent of choice in people with newly diagnosed type 2 diabetes, unless contraindicated.
- Dose adjustments and/or additional agents should be instituted to achieve target A1C within 3 to 6 months. Choice of second-line antihyperglycemic agents should be made based on individual patient characteristics, patient preferences, any contraindications to the drug, glucose-lowering efficacy, risk of hypoglycemia, affordability/access, effect on body weight and other factors.
- In people with clinical cardiovascular (CV) disease in whom A1C targets are not achieved with existing pharmacotherapy, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to antihyperglycemic therapy to reduce CV risk.
- In people without clinical CV disease in whom A1C target is not achieved with current therapy, if affordability and access are not barriers, people with type 2 diabetes and their providers who are concerned about hypoglycemia and weight gain may prefer an incretin agent (DPP-4 inhibitor or GLP-1 receptor agonist) and/or an SGLT2 inhibitor to other agents as they improve glycemic control with a low risk of hypoglycemia and weight gain.
- In people receiving an antihyperglycemic regimen containing insulin, in whom glycemic targets are not achieved, the addition of a GLP-1 receptor agonist, DPP-4 inhibitor or SGLT2 inhibitor may be considered before adding or intensifying prandial insulin therapy to improve glycemic control with less weight gain and comparable or lower hypoglycemia risk.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Some people who have type 2 diabetes can achieve their target blood glucose levels with nutrition guidance and physical activity alone, but most also need glucose-lowering medications. The decision about which medications are best for you depends on many factors, including your blood glucose level, symptoms, other health problems you have and affordability of medications. Your health-care provider may even combine medications that act differently on your body to help you control your blood glucose.
- Glucose-lowering medications for type 2 diabetes include:
  First-line glucose-lowering medication:
  - **Metformin:** Metformin is generally the first choice for people with type 2 diabetes because of its safety, low cost and possible heart benefits. It works by making your body respond better to insulin so that your body uses insulin more effectively. Metformin also lowers glucose production from the liver. Nausea and diarrhea are possible side effects and usually go away within 1 to 2 weeks as your body gets used to the medicine. It is associated with a low risk of hypoglycemia and does not cause weight gain.
  - If metformin and healthy behaviour changes are not enough to control your blood glucose level, other medications can be added.

  Second-line glucose-lowering medication:
  - **DPP-4 inhibitors:** These medications work to lower blood glucose by increasing insulin levels after meals and lowering glucagon levels (a hormone that raises blood glucose). They do not cause weight gain and are associated with a low risk of hypoglycemia.
  - **GLP-1 receptor agonists:** These injectable medications act when blood glucose increases after eating. They increase insulin levels, which helps lower blood glucose and lower glucagon levels (a hormone that raises blood glucose). They also slow digestion and reduce appetite. Possible side effects include nausea, which usually goes away with time. They are associated with weight loss and a low risk of hypoglycemia.
  - **SGLT2 inhibitors:** These medications work by eliminating glucose into the urine. Side effects may include genital yeast infections, urinary tract infections, increased urination and low blood pressure. They are associated with weight loss and a low risk of hypoglycemia.
  - **Insulin secretagogues (meglitinides, sulfonylureas):** These medications help your pancreas release more insulin. Possible side effects include hypoglycemia and weight gain.
  - **Thiazolidinediones:** Like metformin, these medications make the body's tissues more sensitive to insulin. Side effects include weight gain and an increased risk of heart failure and fractures.
  - **Insulin therapy:** Some people who have type 2 diabetes need insulin therapy as well. Depending on your needs, your health-care provider may prescribe a mixture of insulin types to use throughout the day and night. Often, people with type 2 diabetes start insulin use with 1 injection of long-acting insulin at night.
- Discuss the pros and cons of different treatment plans with your health-care provider. Together, you can decide which medication is best for you after considering many factors, including costs and other aspects of your health.

Conflict of interest statements can be found on page S100.

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Introduction

People with type 2 diabetes form a heterogeneous group. Consequently, treatment regimens and therapeutic targets should be individualized. The treatment of type 2 diabetes involves a multipronged approach that aims to treat and prevent symptoms of hyperglycemia, such as dehydration, fatigue, polyuria, infections and hyperosmolar states; and to reduce the risks of cardiovascular (CV) and microvascular complications (1). This includes healthy behaviour interventions (see Reducing the Risk of Diabetes chapter, p. S20; Cardiovascular Protection in People with Diabetes chapter, p. S162) and antihyperglycemic medications. This chapter provides updated recommendations for the approach to antihyperglycemic therapy and selection of pharmaceutical agents. The number of available antihyperglycemic agents is ever expanding, requiring the healthcare provider to consider many of the following factors when choosing medications: degree of hyperglycemia, medication efficacy for reducing diabetes complications (microvascular and/or CV) and lowering glucose, medication effects on the risk of hypoglycemia, body weight, other side effects, concomitant medical conditions, ability to adhere to regimen, broader health and social needs, affordability of medications, and patient values and preferences. Recommendations in this chapter are based on a rigorous and careful review of the evidence regarding the efficacy and adverse effects of available medications on clinically important outcomes.

Treatment Regimens

Newly diagnosed type 2 diabetes

Individuals presenting with newly diagnosed type 2 diabetes require a multifaceted treatment plan. This includes diabetes education by an interprofessional team (see Self-Management Education and Support chapter, p. S36), healthy behaviour interventions (diet and physical activity, smoking cessation) with a target of 5% to 10% weight loss for overweight individuals (see Weight Management in Diabetes chapter, p. S124; Cardiovascular Protection in People with Diabetes chapter, p. S162), and screening for complications. It should be emphasized to people with type 2 diabetes that healthy behaviour interventions and weight loss can lead to withdrawal of antihyperglycemic medication and even remission of type 2 diabetes in some cases (2). The Look AHEAD (Action for Health in Diabetes) trial showed that an intensive healthy behaviour intervention resulted in a significantly greater weight loss and likelihood of diabetes remission after 1 year compared to standard care, with the greatest benefit seen in persons with new-onset type 2 diabetes (21.2% remission rate) (2). Antihyperglycemic therapy with metformin may also be initiated at diagnosis, depending on the current and target glycated hemoglobin (A1C).

The treatment of hyperglycemia should begin with the establishment of a target A1C which, in most cases, will be ≤7.0% as this has been shown to reduce long-term microvascular complications in newly diagnosed people with type 2 diabetes (3). A1C targets may be higher (up to 8.5%) if the benefits of intensive glycemic control are unlikely to outweigh the risks and burden, such as in individuals with limited life expectancy, high risk of hypoglycemia, multimorbidity, or based on the values and preferences of the person with diabetes (see Targets for Glycemic Control chapter, p. S42 for recommendations). It should be emphasized to people with type 2 diabetes that reductions in A1C levels are associated with better outcomes even if recommended glycemic targets cannot be reached, and inability to achieve A1C target should not be considered a treatment failure (3,4).

If the A1C level at diagnosis is less than 1.5% above target and the person with type 2 diabetes lacks metabolic decompensation and/or symptoms of hyperglycemia, the first line of treatment should be healthy behaviour interventions (see Reducing the Risk of Diabetes chapter, p. S20). If healthy behaviour interventions are insufficient to achieve target A1C levels within 3 months, they should be combined with antihyperglycemic medications. In the face of significant hyperglycemia (i.e. A1C >1.5% above target), pharmacotherapy is usually required at diagnosis concurrent with healthy behaviour interventions. People who have evidence of metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) and/or symptomatic hyperglycemia should be started immediately on insulin, regardless of A1C level. Insulin may later be tapered or discontinued once stability is achieved.

In general, A1C will decrease by about 0.5% to 1.5% with monotherapy, varying with the specific agent used and the baseline A1C level. By and large, the higher the baseline A1C, the greater the A1C reduction seen for each given agent. The maximum effect of noninsulin antihyperglycemic agent monotherapy is observed by 3 to 6 months (5,6).

Initial combination therapy (with or without insulin) may be required in settings of more severe hyperglycemia and/or metabolic decompensation to provide a more rapid and larger decrease in A1C (7–11). Evidence indicates that initial combination of metformin with another agent is associated with an additional mean 0.4% to 1.0% reduction in A1C and a relative 40% higher chance of achieving A1C <7.0% after 6 months compared to metformin alone (7–9,12).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (13–17).

Table 1 lists all the available classes of antihyperglycemic therapies. These include insulin and noninsulin therapies. Unless contraindicated, metformin should be the initial pharmacotherapy in people with type 2 diabetes. Contraindications include chronic kidney disease (CKD) stage 4 to 5 (eGFR <30 mL/min) and hepatic failure. The recommendation to use metformin as the initial agent in most people is based on its efficacy in lowering A1C, its relatively mild side effect profile, long-term safety track record, affordability, negligible risk of hypoglycemia and lack of weight gain. Compared to sulfonylureas, metformin monotherapy has comparable A1C-lowering effects, but better glycemic durability (18), a lower risk of hypoglycemia (19), less weight gain (19,20) and lower CV risk (20). Metformin is associated with less weight gain than thiazolidinediones (21), and has better A1C lowering and weight loss than DPP-4 inhibitors (19). The demonstrated CV benefit of metformin monotherapy in newly diagnosed participants who were overweight in the UKPDS trial (17) is also cited as a reason to select metformin as first-line treatment, although other evidence from a meta-analysis of metformin trials has been equivocal on this matter (21,22). Metformin should be started at a low dose and gradually increased over several weeks to minimize the risk of gastrointestinal side effects. If metformin is contraindicated or if initial combination therapy is required, then a second agent should be chosen based on individual patient characteristics and the efficacy and safety profile of other agents (see Table 1 and Figure 2). DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors should be considered over other antihyperglycemic agents as they are associated with less hypoglycemia and weight gain (19,23–27), provided there are no contraindications and no barriers to affordability or access.

Insulin may be used at diagnosis in individuals with marked hyperglycemia and can also be used temporarily during illness, pregnancy, stress or for a medical procedure or surgery. The use of intensive insulin therapy may lead to partial recovery of beta cell function when used in people with metabolic decompensation, and studies suggest that early insulin treatment may induce remission in people

Table 1
Antihyperglycemic agents for use in type 2 diabetes

Class and mechanism of action	Drug	Cost	A1C lowering*	Hypoglycemia	Weight	Effect on primary CVD outcomes	Other therapeutic considerations
First Line							
Biguanide: Enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase	Metformin Metformin extended-release	$	Approx. 1.0†	Negligible risk as monotherapy	Neutral	Reduction in myocardial infarction in overweight individuals	• GI side effects • Vitamin B12 deficiency • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR 30 to 60 mL/min
Second Line							
Incretin: Increases glucose-dependent insulin release, slows gastric emptying, inhibits glucagon release	**DPP-4 inhibitors** Alogliptin Linagliptin Saxagliptin Sitagliptin	$$$	0.5 to 0.7	Negligible risk as monotherapy	Neutral	Neutral (for alogliptin, saxagliptin and sitagliptin)	• Rare cases of pancreatitis • Rare cases of severe joint pain • Caution with saxagliptin in participants with heart failure
	GLP-1 receptor agonists** *Short-acting* Exenatide Lixisenatide *Longer-acting* Dulaglutide Exenatide extended-release Liraglutide	$$$$	1.0	Negligible risk as monotherapy	Loss of 1.6 to 3 kg	Reduction in MACE‡ and CV death in participants with clinical CVD (for liraglutide) Neutral (for exenatide ER, lixisenatide)	• Subcutaneous injection • Nausea, vomiting, diarrhea • Less A1C lowering with short-acting agents than longer-acting agents • Rare cases of acute gallstone disease • Reduced progression of nephropathy with liraglutide • Contraindicated with personal/family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
SGLT-2 inhibitors: Inhibits SGLT-2 transport protein to prevent glucose reabsorption by the kidney	Canagliflozin Dapagliflozin Empagliflozin	$$$	0.4 to 0.7	Negligible risk as monotherapy	Loss of 2 to 3 kg	Reduction in MACE‡ (empagliflozin and canagliflozin) and CV death (empagliflozin) in participants with clinical CVD	• Reduced progression of nephropathy and reduction in heart failure in participants with clinical CVD with empagliflozin and canagliflozin • Genital mycotic infections • Urinary tract infections • Hypotension • Small increase in LDL-C • Rare cases of diabetic ketoacidosis (which may occur without hyperglycemia) • Increased risk of fractures with canagliflozin Increased risk of lower extremity amputation with canagliflozin (avoid if prior amputation) • Dapagliflozin not to be used with bladder cancer • Reports of acute kidney injury with canagliflozin and dapagliflozin • Contraindicated if CrCl/eGFR <45 mL/min (canagliflozin, empagliflozin) or <60 mL/min (dapagliflozin) • Caution with renal dysfunction, loop diuretics, the elderly • Treatment should be withheld prior to major surgery or with serious illness or infections
Alpha-glucosidase inhibitor: Inhibits pancreatic α-amylase and intestinal α-glucosidase	Acarbose	$$	0.7 to 0.8§	Negligible risk as monotherapy	Neutral	—	• GI side effects common • Requires 3 times daily dosing

(*continued on next page*)

Table 1
(*continued*)

Class and mechanism of action	Drug	Cost	A1C lowering*	Hypoglycemia	Weight	Effect on primary CVD outcomes	Other therapeutic considerations
Insulin: Activates insulin receptors to regulate metabolism of carbohydrate, fat, and protein	**Bolus (prandial) Insulins** *Rapid-acting analogues* Aspart Aspart (faster-acting) Glulisine Lispro U-100 Lispro U-200 *Short-acting* Regular **Basal Insulins** *Intermediate-acting* NPH *Long-acting analogues* Degludec U-100 Degludec U-200 Detemir Glargine U-100 Glargine U-100 (biosimilar) Glargine U-300 **Premixed Insulins** Premixed regular-NPH Biphasic insulin aspart Lispro/lispro protamine suspension	$ to $$$$	0.9 to 1.2 or more	Significant risk	Gain of 4 to 5 kg Gain of 0 to 0.4 kg for long-acting analogue alone	Neutral (for glargine and degludec)	• Potentially greatest A1C reduction and no maximum dose • Numerous formulations and delivery systems, allows for regimen flexibility
Insulin secretagogue: Activates sulfonylurea receptor on β-cell to stimulate endogenous insulin secretion	**Sulfonylureas** Gliclazide Gliclazide modified-release Glimepiride Glyburide (note: chlorpropamide and tolbutamide are still available in Canada, but rarely used)	$	0.7 to 1.3	Minimal/ moderate risk Moderate risk Moderate risk	Gain of 1.5 to 2.5 kg	—	• Gliclazide preferred over glyburide due to lower risk of hypoglycemia, CV events, mortality • Relatively rapid BG-lowering response • Postprandial glycemia is especially reduced by meglitinides • Meglitinides require 3 times daily dosing • Repaglinide contraindicated when co-administered with clopidogrel or with gemfibrozil
	Meglitinides Repaglinide	$$	0.7 to 1.1	Minimal/ moderate risk	Gain of 0.7 to 1.8 kg	—	
Thiazolidinedione (TZD): Enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator-activated receptor-activated receptor- gamma receptors	Pioglitazone Rosiglitazone	$$$	0.8 to 0.9	Negligible risk as monotherapy	Gain of 2.5 to 5 kg	Neutral (for pioglitazone)	• Mild increase in HDL-C • May induce edema and/or congestive heart failure • Rare occurrence of macular edema • Higher occurrence of fractures • Pioglitazone not to be used with bladder cancer • Controversy regarding MI risk for rosiglitazone
Weight loss agent: Inhibits lipase	Orlistat	$$$	0.2 to 0.4	Negligible risk as monotherapy	Loss of 3 to 4 kg	—	• Promotes weight loss • Can cause diarrhea and other GI side effects • Requires 3 times daily dosing

A1C, glycated hemoglobin; *BG*, blood glucose; *CrCl*, creatinine clearance; *CV*, cardiovascular; *CVD*, cardiovascular disease; *eGFR*, estimated glomerular filtration rate; *GI*, gastrointestinal; *HDL-C*, high density lipoprotein cholesterol; *LDL-C*, low density lipoprotein cholesterol; *MI*; myocardial infarct.

* Maruthur et al 2016 (19); Mearns et al 2015 (24); Liu et al 2012 (23).

** Semaglutide received Health Canada approval after these guidelines were in press.

† A1C lowering vs. placebo, Sherifali et al 2010 (6).

‡ *MACE*, major adverse cardiovascular event.

§ Based on data from 2 trials in <100 patients.

with newly diagnosed type 2 diabetes (28,29–31). Trials of this approach are ongoing.

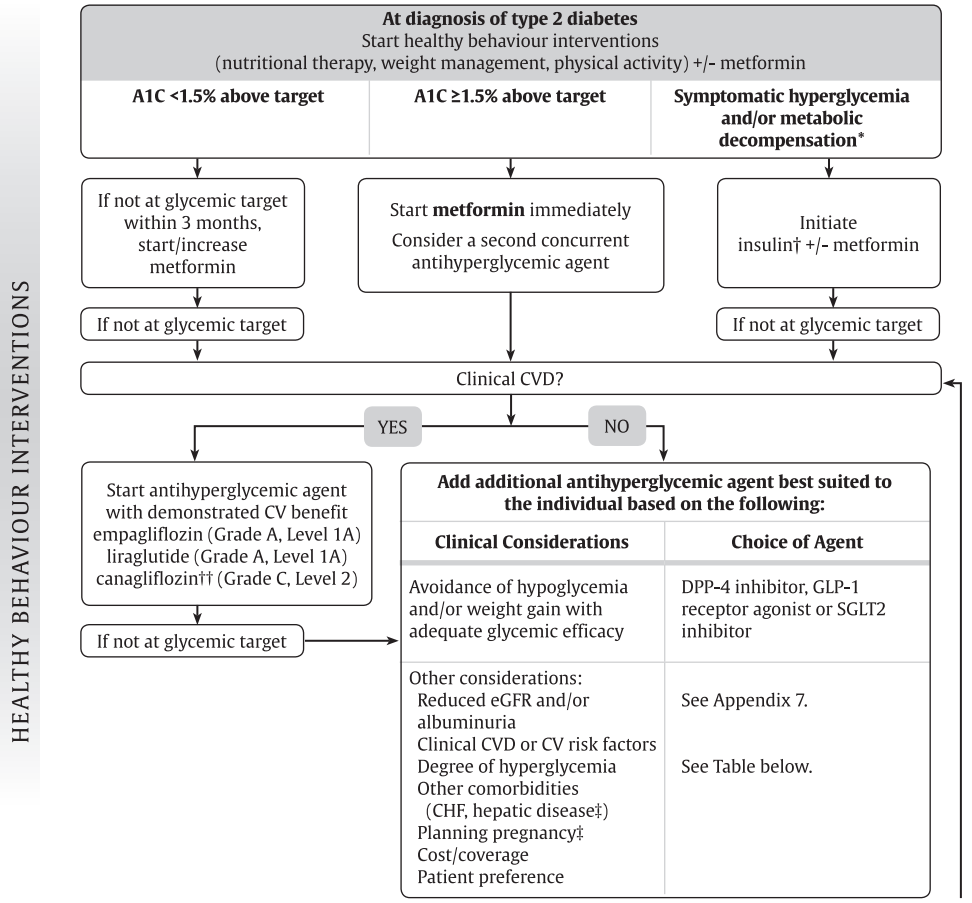
Treatment advancement in people with pre-existing type 2 diabetes

The natural history of type 2 diabetes is that of ongoing beta cell function decline, so blood glucose (BG) levels often increase over time even with excellent adherence to healthy behaviours and therapeutic regimens (32). Treatment must be responsive as therapeutic requirements may increase with longer duration of disease. If A1C target is not achieved or maintained with current pharmacotherapy, treatment intensification is often required. A review of potential precipitants of increasing A1C (e.g. infection, ischemia) and medication adherence should first be conducted, and current therapy may need to be modified if there are significant barriers to adherence. Dose adjustments and/or additional antihyperglycemic medications should be instituted to achieve A1C target within 3 to 6 months, to avoid clinical inertia and manage ongoing disease progression (33). Healthy behaviour interventions, including nutritional therapy and physical activity, should continue to be optimized while pharmacotherapy is being intensified. Metformin should be continued with other agents unless contraindicated.

In general, when combining antihyperglycemic agents with or without insulin, classes of agents that have different mechanisms of action should be used. Simultaneous use of agents within the same class and/or from different classes but with similar mechanisms of action (e.g. sulfonylureas and meglitinides or DPP-4 inhibitors and GLP-1 receptor agonists) is currently untested, may be less effective at improving glycemia and is not recommended at this time. Table 1 identifies the mechanism of action for all classes of antihyperglycemic agents to aid the reader in avoiding the selection of agents with overlapping mechanisms.

Effects of Antihyperglycemic Agents on Microvascular and Cardiovascular Complications

In deciding upon which agent to add after metformin, there must be consideration of both short-term effects on glycemic control and long-term effects on clinical complications. Agents with evidence demonstrating the ability to not only lower glucose levels but also reduce the longer-term risk of microvascular and/or CV complications should be prioritized. While intensive glycemic control with a variety of agents is associated with a reduction in microvascular complications (3) and possibly CV complications (34) (see Targets for Glycemic Control chapter, p. S42), Table 1 highlights agent-specific effects on CV or microvascular complications (e.g. CKD) based on trials where glycemic differences between treatment arms were minimized.



* May include dehydration, DKA, HHS
† Insulin may be required at any point for symptomatic hyperglycemia/metabolic decompensation or if unable to achieve glycemic targets with other antihyperglycemic agents
†† Avoid in people with prior lower extremity amputation
‡ See product monographs

Figure 1. Management of hyperglycemia in type 2 diabetes.
A1C, glycated hemoglobin; *CHF*, congestive heart failure; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DKA*, diabetic ketoacidosis; *eGFR*, estimated glomerular filtration rate; *HHS*, hyperosmolar hyperglycemic state.

Add additional antihyperglycemic agent best suited to the individual by prioritizing patient characteristics (Classes listed in alphabetical order)

Class*	Effect on CVD outcomes	Hypo-glycemia	Weight	Relative A1C lowering when added to metformin	Other therapeutic considerations	Cost
GLP-1 receptor agonists	lira: Superiority in people with type 2 diabetes with clinical CVD exenatide LAR & lixi: Neutral	Rare	↓↓	↓↓ to ↓↓↓	GI side-effects Gallstone disease Contraindicated with personal/family history of medullary thyroid cancer or MEN 2 Requires subcutaneous injection	$$$$
SGLT2 inhibitors	cana & empa: Superiority in people with type 2 diabetes with clinical CVD	Rare	↓↓	↓↓ to ↓↓↓	Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis (may occur with no hyperglycemia). Increased risk of fractures and amputations with canagliflozin Reduced progression of nephropathy and CHF hospitalizations with empagliflozin and canagliflozin in persons with clinical CVD	$$$
DPP-4 Inhibitors	Neutral (alo, saxa, sita)	Rare	Neutral	↓↓	Caution with saxagliptin in heart failure Rare joint pain	$$$
Insulin	glar: Neutral degludec: noninferior to glar	Yes	↑↑	↓↓ to ↓↓↓↓	No dose ceiling, flexible regimens Requires subcutaneous injection	$-$$$$
Thiazolidinediones	Neutral	Rare	↑↑	↓↓	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Alpha-glucosidase inhibitors (acarbose)		Rare	Neutral	↓	GI side-effects common Requires 3 times daily dosing	$$
Insulin secretatogue: Meglitinide		Yes	↑	↓↓	More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing	$$
Sulfonylurea		Yes	↑	↓↓	Gliclazide and glimepiride associated with less hypoglycemia than glyburide Poor durability	$
Weight loss agent (orlistat)		None	↓	↓	GI side effects Requires 3 times daily dosing	$$$

alo, alogliptin; *cana,* canagliflozin; *empa,* empagliflozin; *glar,* glargine; *lira,* liraglutide; *exe LAR,* exenatide long-acting release; *lixi,* lixisenatide; *saxa,* saxagliptin; *sita,* sitagliptin.

If not at glycemic targets

Add another antihyperglycemic agent from a different class and/or add/intensify insulin regimen
Make timely adjustments to attain target A1C within 3-6 months

* Listed by CV outcome data

Figure. 1. (*continued*)

The effect of exogenous insulin on the risk of CV complications has been shown to be neutral (35,36). The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial studied the use of basal insulin titrated to a FBG of <5.3 mmol/L in people at high CV risk with prediabetes or early type 2 diabetes over 6 years. There was a neutral effect on CV outcomes and cancer, and a slight increase in hypoglycemia and weight (36,37).

Earlier trials evaluated effects of thiazolidinediones on CV events. Meta-analyses of smaller studies suggested possible higher risk of myocardial infarction (MI) with rosiglitazone (38,39); however, CV events were not significantly increased in a larger randomized clinical trial (40,41). Conversely, the evidence for pioglitazone suggests a possible reduced risk of CV events, but the primary CV outcome was neutral (42,43). While these agents have comparable glucose-lowering effects to other drugs, the edema, weight gain, risk of congestive heart failure (CHF) (44), increased risk of fractures (45,46) and inconsistent data regarding MI risk with rosiglitazone (38–40) and bladder cancer risk with

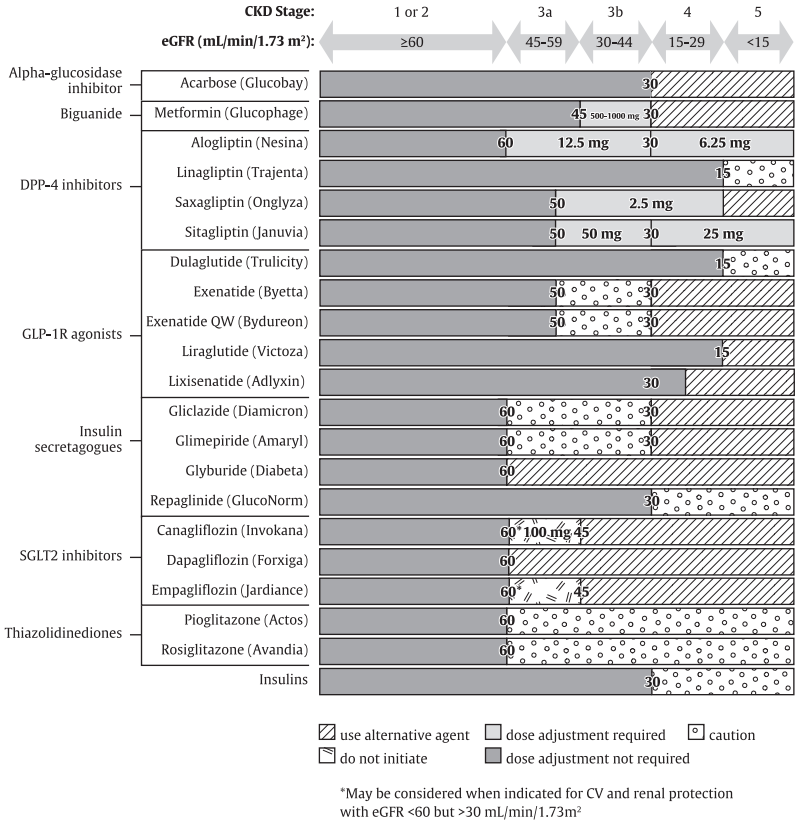


Figure 2. Antihyperglycemic medications and renal function. Based on product monograph precautions. *CKD,* chronic kidney disease; *CV*, cardiovascular; *GFR*, glomerular filtration rate; *TZD*, thiazolidinedione.

pioglitazone significantly limit the clinical utility of this drug class (47,48).

Based on controversies regarding rosiglitazone, in 2008, the United States Food and Drug Administration (FDA) required that all new antidiabetic therapies undergo evaluation for CV safety at the time of approval. Subsequently, several industry-sponsored placebo-controlled trials were initiated to evaluate CV outcomes of drugs from 3 newer classes: DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors (see Table 2). Trial durations are from 1.5 to 5 years, and the majority of participants had established type 2 diabetes and either clinical CV disease or multiple CV risk factors. Therefore, findings from these trials are directly relevant to people with established type 2 diabetes and clinical CV disease or multiple risk factors. Studies have not evaluated whether findings are generalizable to people with new-onset type 2 diabetes or those at average or lower CV risk.

Three DPP-4 inhibitor trials have been completed (Table 2). None have shown inferiority or superiority compared to placebo for the risk of major CV events (49,50). Saxagliptin was associated with an increased incidence of hospitalization for heart failure (50) that has yet to be fully explained and, therefore, this agent is not recommended in people with a history of CHF, especially in people who also have renal impairment and/or history of MI. There was a non-statistically significant increase in hospitalizations for CHF with alogliptin in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial (49) and there is limited experience treating people with a history of CHF with linagliptin; therefore, these agents should be used with caution in that setting. Moreover, a secondary analysis of the data suggested a possibly higher relative risk of unstable angina and all-cause mortality with saxagliptin in those under 65 years (51). The significance of these findings is unclear and further studies are needed. The GLP-1 receptor agonist, lixisenatide, was also shown to be non-inferior to placebo after a median 2.1 years of follow up (52).

Three approved and one unapproved antihyperglycemic agent, thus far, have shown benefit in reducing major CV outcomes in individuals with clinical CVD, the SGLT2 inhibitors empagliflozin (53) and canagliflozin (54), and the GLP-1 receptor agonists liraglutide (55) and semaglutide (56). The Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) included 7,020 people with type 2 diabetes and clinical CVD (defined by ≥1 of the following: MI >2 months prior, multivessel CAD, single-vessel CAD with positive stress test or unstable angina hospitalization in prior year, unstable angina >2 months prior and evidence of CAD, stroke >2 months prior, occlusive peripheral artery disease), most of whom (78%) were already on antihyperglycemic therapy and 82% had diabetes for more than 5 years. Those treated with empagliflozin had significantly fewer CV events (CV death, nonfatal MI, nonfatal stroke) compared to placebo-treated participants after a median 3.1 years follow up (10.5% vs. 12.1%, hazard ratio [HR], 0.86, p<0.001 for noninferiority, p=0.04 for superiority), which was driven by a significant decrease in CV mortality as nonfatal events were not significantly reduced. In a secondary analysis, empagliflozin was associated with a significant reduction in hospitalizations for CHF (4.1 vs. 2.7%, HR 0.65, 95% confidence interval [CI] 0.50–0.85) (53,57). Recent meta-analyses of SGLT2 inhibitors confirmed a significant benefit of this class of agents on major CV outcomes, which was largely driven by EMPA-REG OUTCOME results (58–60).

The CANagliflozin cardioVascular Assessment Study (CANVAS) program, which integrated findings from 2 placebo-controlled trials (CANVAS and CANVAS-R), evaluated the CV effects of canagliflozin (54). The trials enrolled 10,142 participants (4,330 in CANVAS and 5,812 in CANVAS-R) with type 2 diabetes (mean duration 13.5 years), who were aged 30 years or older with symptomatic

Table 2
Major clinical outcome trial characteristics for antihyperglycemic agents

Study	Clinicaltrials.gov	Agent (Dose) (n)	Age (yrs)	Men	DM (yrs)	A1C (%) Start	A1C (%) End	Follow up (yrs)	Completed	Results*
Dipeptidyl Peptidase-4 Inhibitors										
EXAMINE (49,145)	NCT00968708	Alogliptin (25 or 12.5 mg) (n=2,701)	61.0†	68%	7.1†	8.0 (±1.1)	-0.33	1.5†	n=2,692 (99%)‡	MACE: 0.96 (UL 1.16)
		Placebo (n=2,679)			7.3†		+0.03		n=2,663 (99%)‡	HF hosp: 1.07 (0.79–1.46)
CARMELINA§	NCT01897532	Linagliptin (5 mg) (n=4,150 estimated)						Estimated completion in 2018		MACE + UA
		Placebo (n=4,150 estimated)								
CAROLINA (143)	NCT01243424	Linagliptin (5 mg) (n=unknown)	64	60%	6.2	7.2		Estimated completion in 2019		MACE + UA
		Glimepiride (1–4 mg) (n=unknown) (total enrolled n=6,051)								
SAVOR-TIMI 53 (50)	NCT01107886	Saxagliptin (5 or 2.5 mg) (n=8,280)	65.1	67%	10.3†	8.0 (±1.4)	7.7	2.1†	n=8,078 (97%)	MACE: 1.00 (0.89–1.12)
		Placebo (n=8,212)	65.0				7.9		n=7,998 (97%)	HF hosp: 1.27 (1.07–1.51)
TECOS (144)	NCT00790205	Sitagliptin (100 or 50 mg) (n=7,332)	65.4	71%	11.6	7.2 (±0.5)	0.29 lower than placebo	3.0†	n=6,972 (95%)	MACE + UA: 0.98 (0.88–1.09)
		Placebo (n=7,339)	65.5	70%					n=6,905 (94%)	HF hosp: 1.00 (0.83–1.20)
GLP-1 receptor agonists										
HARMONY Outcomes§	NCT02465515	Albiglutide (30 or 50 mg) (n=unknown) estimated enrolment 9,400						Estimated completion in 2018		MACE
		Placebo (n=unknown)								
REWIND§	NCT01394952	Dulaglutide(1.5 mg) (n=unknown) total enrolled n=9,622						Estimated completion in 2018		MACE
		Placebo (n=unknown)								
EXSCEL (146)	NCT01144338	Exenatide (2 mg) (n=7,356)	60.2†	62%	12.0†	8.0†	0.53 lower than placebo	3.8†	n=7,094 (96%)	MACE: 0.91 (0.83–1.00)
		Placebo (n=7,396)	60.2†	62%					n=7,093 (96%)	CV death: 0.88 (0.76–1.02) HF hosp: 0.94 (0.78–1.13)
FREEDOM-CVO§	NCT01455896	ITCA 650 (Exenatide in DUROS) (60 µg) (n=unknown) estimated enrolment n=4,000						Study completed April 2016		MACE + UA: results not released yet
		Placebo (n=unknown)								
LEADER (55)	NCT01179048	Liraglutide (1.8 mg) (n=4,668)	64.2	65%	12.8	8.7 (±1.5)	0.40 lower than placebo	3.8†	n=4,529 (97%)	MACE: 0.87 (0.78–0.97)
		Placebo (n=4,672)	64.4	64%					n=4,513 (97%)	CV death: 0.78 (0.66–0.93) HF hosp: 0.87 (0.73–1.05)
ELIXA (52)	NCT01147250	Lixisenatide (20 µg) (n=3,034)	59.9	70%	9.2	7.7	0.27 lower than placebo	2.1†	n=2,922 (96%)	MACE + UA: 1.02 (0.89–1.17)
		Placebo (n=3,034)	60.6	69%	9.4	7.6			n=2,916 (96%)	HF hosp: 0.96 (0.75–1.23)
PIONEER 6§	NCT02692716	Semaglutide (not stated) (unknown) estimated enrolment n=3,176						Estimated completion in 2018		MACE
		Placebo (n=unknown)								
SUSTAIN 6 (56)	NCT01720446	Semaglutide (0.5 mg) (n=826)	64.6	60%	14.3	8.7	-1.1	2.1†	1,623 (99%)	MACE: 0.74 (0.58–0.95)
		Semaglutide (1.0 mg) (n=822)	64.7	63%	14.1	8.7	-1.4			HF hosp: 1.11 (0.77–1.61)
		Placebo (n=1,649)	64.6	60%	13.6	8.7	-0.4		n=1,609 (98%)	Retinopathy: 1.76 (1.11–2.78)

(*continued on next page*)

Table 2
(*continued*)

Study	Clinicaltrials.gov	Agent (Dose) (n)	Age (yrs)	Men	DM (yrs)	A1C (%) Start	A1C (%) End	Follow-up (yrs)	Completed	Results*
Sodium-glucose co-transporter-2 inhibitors										
CANVAS (54)	NCT01032629	Canagliflozin (100 mg) (n=1,445)	62.4	66%	13.4	8.2 (±0.9)		5.7		MACE: 0.88 (0.75–1.03)
		Canagliflozin (300 mg) (1,444)								HF hosp: 0.77 (0.55–1.08)
		Placebo (1,444)								
CANVAS-R (54)	NCT01989754	Canagliflozin (300 mg) (n=2,907)	64.0	63%	13.7	8.3 (±1.0)		2.1		Prog Alb: 0.64 (0.57–0.73)
		Placebo (n=2,905)								MACE: 0.82 (0.66–1.01)
CANVAS Program (54)		Canagliflozin (100 or 300 mg) (n=5,795)	63.2	65%	13.5	8.2 (±0.9)	0.58 lower than placebo	3.6	n=9,734 (96%)	MACE: 0.86 (0.75–0.97)
		Placebo (n=4,347)	63.4	63%	13.7	8.2 (±0.9)				Prog Alb: 0.73 (0.67–0.79) HF hosp: 0.67 (0.52–0.87) LL amp: 1.97 (1.41–2.75)
CREDENCE§	NCT02065791	Canagliflozin (100 mg) (n=unknown) estimated enrolment n=4,200						Estimated completion in 2019		ESRD, 2xSCr, renal or CV death
		Placebo (unknown)								MACE + HF + UA
Dapa-CKD§	NCT03036150	Dapagliflozin (5 or 10 mg) (n=unknown) estimated enrollment n=4,000						Estimated completion in 2020		≥50% ⇓ eGFR, ESRD, renal or CV death
		Placebo (n=unknown)								
Dapa-HF§	NCT03036124	Dapagliflozin (5 or 10 mg) (n=unknown) estimated enrolment n=4,500						Estimated completion in 2019		CV death or HF hosp
		Placebo (n=unknown)								
DECLARE-TIMI 58§	NCT01730534	Dapagliflozin (10 mg) (n=unknown) total enrolled n=17,276						Estimated completion in 2019		MACE
		Placebo (n=unknown)								
EMPA-REG Outcome (53,57)	NCT01131676	Empagliflozin 10 mg (n=2,345)	63.0	71%	57% had diabetes >10 yrs	~8.0	0.24 lower	3.1†	n=2,264 (97%)	MACE: 0.86 (0.74–0.99) CV death: 0.62 (0.49–0.77)
		Empagliflozin (25 mg) (n=2,342)	63.2	72%			0.36 lower		n=2,279 (97%)	HF hosp: 0.65 (0.50–0.85)
		Placebo (n=2,333)	63.2	72%			@206 wks		n=2,266 (97%)	
EMPEROR-Preserved§	NCT03057951	Empagliflozin (10 mg) (n=unknown) estimated enrollment n=4,126						Estimated completion in 2020		CV death or HF hosp
		Placebo (n=unknown)								
EMPEROR-Reduced§	NCT03057977	Empagliflozin (not stated) (n=unknown) estimated enrolment n=2,850						Estimated completion in 2020		CV death or HF hosp
		Placebo (n=unknown)								
VERTIS CV§	NCT01986881	Ertugliflozin (15 mg) (n=4,000 estimated)						Estimated completion in 2019		MACE
		Placebo (n=4,000 estimated)								

2xScr, doubling of serum creatinine; *≥50%⇓eGFR*, minimum 50% decline in estimated glomerular filtration rate; *CV Death*, death from cardiovascular causes; *ESRD*, end stage renal disease; *HF hosp*, hospitalization for heart failure; *LL Amp*, lower limb amputation; *MACE*, major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke); *MACE + UA*, MACE plus hospitalization for unstable angina; *Prog Alb*, progression of albuminuria; *UL*, upper limit of 95% confidence interval.

* Primary outcome reported first hazard ratio (95% confidence interval).

† Median

‡ Vital status known (number of participants who completed protocol not reported).

§ No peer-reviewed publications, data taken from Clincaltrials.gov.

CVD (symptomatic atherosclerotic vascular disease (coronary, cerebrovascular or peripheral) (66%) or 50 years or older with at least 2 CV risk factors (duration of diabetes ≥10 years, systolic BP >140 mmHg while on ≥1 antihypertensive agent, current smoker, microalbuminuria, macroalbuminuria or HDL cholesterol <1.0 mmol/L) (34%). Over a median follow up of 2.4 years, significantly fewer persons randomized to canagliflozin than placebo had the primary outcome of CV death, nonfatal MI or nonfatal stroke (26.9 vs. 31.5 per 1,000 person-years respectively; HR 0.86, 95% CI 0.75–0.97, p<0.001 for noninferiority and p=0.02 for superiority). There were no statistical differences in the individual components of the composite outcome. There was a reduction in hospitalization for heart failure and in several adverse renal outcomes; however, these were considered exploratory outcomes due to pre-specified rules of evidence hierarchy. While one-third of participants did not have CVD, a significant decrease in the primary endpoint was only found in those with CVD. Therefore, as with other CV outcome trials, these results largely apply to people with type 2 diabetes requiring add-on antihyperglycemic therapy who have established clinical CVD. Canagliflozin was also associated with an increase in fracture rates (HR 1.26, 95% CI 1.04–1.52), and higher rates of genital infections and volume depletion. Importantly, canagliflozin was associated with doubling in the risk of lower extremity amputation (HR 1.97, 95% CI 1.41–2.75). This risk was strongest in participants with a prior amputation. Canagliflozin should, therefore, be avoided in people with a prior amputation, as the harms appear to be greater than the benefits in that population.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial enrolled 9,340 participants with longstanding type 2 diabetes (median duration 12.8 years) and 88% were on antihyperglycemic therapy at baseline (55). The majority of included participants (81%) were ≥50 years of age on pre-existing antihyperglycemic therapy with at least 1 CV condition (coronary heart disease [CHD], cerebrovascular disease, peripheral arterial disease, CHF or stage 3 or higher CKD). Over a median follow up of 3.8 years, fewer participants in the liraglutide arm compared to placebo had the primary endpoint of CV death, nonfatal MI or nonfatal stroke (13% vs. 14.9%, respectively; HR 0.87, 95% CI 0.78–0.97), fulfilling the statistical criteria for both noninferiority (p<0.001) and superiority (p=0.01). While the LEADER trial included some people with CV risk factors only, over 80% of participants had cardiovascular disease (CVD) and only 10.5% of the primary events occurred in those without clinical disease. Therefore results are most applicable to people with type 2 diabetes with clinical CVD requiring add-on antihyperglycemic therapy.

The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) enrolled 3,297 participants with a mean duration of type 2 diabetes of 13.9 years (56). At baseline, 98% were on antihyperglycemic therapy and 83% had established CVD or stage 3 or higher CKD. After a median follow up of 2.1 years, the primary composite outcome of CV death, nonfatal MI or nonfatal stroke occurred in 6.6% of participants treated with semaglutide and 8.9% of participants treated with placebo (HR 0.74, 95% CI 0.58–0.95), fulfilling statistical criteria for noninferiority (p<0.001); a non-pre-specified test for superiority was also significant (p=0.02). There was, however, a higher rate of diabetic retinopathy complications in the semaglutide group compared to placebo group (3.0% vs. 1.8%, HR 1.76; 95% CI 1.11–2.78; p=0.02). It is unclear at this time if there is a direct effect of semaglutide or other explanations for this unexpected difference in retinopathy complication rates, although the risk appeared greatest in individuals with pre-existing retinopathy and rapid lowering of A1C.

All 4 trials reported lower rates of kidney disease progression in the treated groups compared to placebo (53,55,56). It should also be noted that the majority of people in these trials had pre-existing CVD and required add-on antihyperglycemic therapy. In addition, because these were placebo-controlled trials, no conclusions can be made about how the cardioprotective properties of empagliflozin, canagliflozin, liraglutide and semaglutide compare to those of other agents. CV outcome trials for other agents are expected to be completed by 2019; therefore, based on evidence to date, a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV outcome benefit should be considered as initial add-on therapy for people with pre-existing type 2 diabetes and clinical CV disease who have not achieved target A1C on existing treatment to reduce CV risk.

A careful review of the methods and findings from these trials was conducted by an independent committee. While primary analyses results were similar for canagliflozin, empagliflozin and liraglutide, it was concluded that the strength of evidence for CV benefit was weaker for canagliflozin than for the other agents. This conclusion was based on three factors. First, in 2012 an interim analysis of the CANVAS study for medication approval necessitated unblinding of study data. A decision was then made to combine this study with the CANVAS-R study, presumably to provide greater power for CV outcomes. The interim unblinding and protocol revision were viewed as potential threats to internal validity, thereby weakening the strength of evidence for benefit. Second, while canagliflozin was associated with a significant decrease in the composite MACE outcome, there was no significant benefit on individual outcomes, such as all-cause or CV mortality. Third, the findings of increased risk of fractures and amputations with canagliflozin treatment in the context of a noninferiority design where the comparator is placebo was particularly concerning, indicating that harms may outweigh benefits. For these reasons, the committee decided that the uncertainty regarding benefits should be acknowledged with a lower grade of recommendation for canagliflozin than for other agents with demonstrated CV benefit.

Effects of Antihyperglycemic Agents on Glycemic Control and Other Short-Term Outcomes

In the absence of evidence for long-term clinical benefit, agents effective at A1C lowering should be considered in terms of both the degree of baseline hyperglycemia needing correction, and any heightened concerns regarding hypoglycemia (e.g. elderly people or those with renal or hepatic dysfunction) (see Diabetes in Older People chapter, p. S283). While most medications added to metformin lower A1C to a similar extent, insulin and insulin secretagogues are associated with higher rates of hypoglycemia than other agents (21,23,24,61). Insulin treatment is recommended for people with metabolic decompensation and/or symptomatic hyperglycemia. In those who are stable, other agent-specific advantages and disadvantages should be weighed as treatment is individualized to best suit the patient's needs and preferences. Each of the agents listed in Table 1 and Figure 1 has advantages and disadvantages to consider. Figure 2 illustrates the basis on which agent selection is influenced by renal function as dictated by product monograph precautions.

Recent meta-analyses have summarized head-to-head comparisons of metformin-based combinations (19,24,62,63). Combinations of metformin with a sulfonylurea, a thiazolidinedione (TZD), an SGLT2 inhibitor and a DPP-4 inhibitor have comparable A1C-lowering effects (19,24,62–66), while the combination of metformin with a GLP-1 receptor agonist reduced A1C more than combination with a DPP-4 inhibitor. TZDs, insulin and sulfonylureas are associated with the most weight gain (1.5 to 5.0 kg) when added to metformin, whereas GLP-1 receptor agonists and SGLT2 inhibitors are associated with weight loss. Hypoglycemia risk is also lower with TZDs, DPP-4 inhibitors, SGLT2 inhibitors and GLP-1 receptor agonists compared to sulfonylureas and insulin

(19,24,62–65,67,68). Network meta-analyses that indirectly compared the net benefits of second- and third-line treatment options have found similar results (21,23,24,69–71). Evidence on comparative effectiveness of acarbose and orlistat is limited, although they are associated with a low risk of hypoglycemia and weight gain. Based on these findings, people on metformin monotherapy requiring treatment intensification and their providers may prefer an incretin agent (DPP-4 inhibitor or GLP-1 receptor agonist), and/or SGLT2 inhibitor to other agents if there are no contraindications and affordability and access are not barriers, as they will improve glycemic control with a low risk of hypoglycemia and weight gain. These agents should be considered before an insulin secretagogue (sulfonylurea or meglitinide) or insulin as add-on therapy in people with a high risk of hypoglycemia (such as elderly people or those with impaired renal function) and/or obesity. The safety of incretin agents, SGLT2 inhibitors and TZDs in pregnancy is unknown; therefore, these agents should be avoided or discontinued in women who are pregnant or planning a pregnancy (see Diabetes and Pregnancy chapter, p. S255).

If a sulfonylurea is added to metformin, gliclazide should be considered as first choice as it is associated with a lower risk of hypoglycemia (67,72), CV events and mortality relative to other sulfonylureas (73). Glimepiride is also associated with a lower risk of CV events and mortality (73), but has a similar rate of hypoglycemia (67,72) compared to other sulfonylureas.

For people already taking metformin and a sulfonylurea, the addition of either a DPP-4 inhibitor, a GLP-1 receptor agonist or SGLT2 inhibitor may be considered as they are associated with effective A1C lowering with less hypoglycemia than insulin or TZDs (21,69,70,74,75); GLP-1 receptor agonists and SGLT2 inhibitors are also associated with weight loss (70,71) (see Weight Management in Diabetes chapter, p. S124). Concurrent addition of 2 antihyperglycemic agents (+/- insulin) to metformin therapy may be considered in settings of more severe hyperglycemia. For instance, the combination of a DPP-4 inhibitor or a GLP-1 receptor agonist and an SGLT2 inhibitor added to metformin has been shown to be as safe and more efficacious at lowering A1C after 24 weeks than either agent alone (76,77).

SGLT2 inhibitors and GLP-1 receptor agonists added to metformin have also been shown to reduce systolic BP compared to metformin alone, and add-on of SGLT2 inhibitors reduce systolic BP more than add-on of sulfonylureas or DPP-4 inhibitors (19).

Insulin Treatment in Type 2 Diabetes

A combination of noninsulin antihyperglycemic agents and insulin often effectively controls glucose levels. Insulin treatment includes long-acting or intermediate-acting insulin analogue injections once or twice daily for basal glycemic control, and bolus injections at mealtimes for prandial glycemic control. Adding insulin to noninsulin antihyperglycemic agent(s) may result in better glycemic control with a smaller dose of insulin (78), and may induce less weight gain and less hypoglycemia than that seen when non-insulin antihyperglycemic agents are stopped and insulin is used alone (79,80). A single injection of an intermediate-acting (NPH) (81) or long-acting insulin analogue (insulin glargine U-100, insulin glargine U-300, insulin detemir or insulin degludec) (82–84) may be added. The addition of bedtime insulin to metformin therapy leads to less weight gain than insulin plus a sulfonylurea or twice-daily NPH insulin (85). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control while trying to avoid hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The mode of insulin administration (continuous subcutaneous infusion vs. injections), the number of insulin injections (1 to 4 per day) and the timing of injections may vary depending on each individual's situation (86).

As type 2 diabetes progresses, insulin requirements will likely increase and higher doses of basal insulin (intermediate-acting or long-acting analogues) may be needed. DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors have been shown to be efficacious at further lowering glucose levels when combined with insulin therapy (87–98). A meta-analysis determined that the addition of a GLP-1 receptor agonist to basal insulin regimens results in greater A1C reduction, more weight loss and less hypoglycemia compared to the addition of bolus insulin (99). A GLP-1 receptor agonist should, therefore, be considered before bolus insulin as add-on therapy in people on basal insulin (with or without other agents) who require antihyperglycemic treatment intensification if there are not barriers to affordability or access.

If glycemic control is suboptimal on treatment regimens that include basal insulin with other agents, bolus insulin at mealtimes (short- or rapid-acting analogues) may be added. Generally, once bolus insulin is introduced into a treatment regimen, either as a separate mealtime bolus or as part of a premixed containing regimen, insulin secretagogues, such as sulfonylureas and meglitinides, should be discontinued. Concomitant therapy with metformin and, if applicable, a GLP-1 receptor agonist, DPP-4 inhibitor or SGLT2 inhibitor should be continued with regimens containing bolus insulin unless contraindicated, to allow for improved glycemic control with less risk of weight gain and hypoglycemia (100).

The reduction in A1C achieved with insulin therapy depends on the dose and number of injections per day (101). A meta-analysis of 12 articles compared basal-bolus and biphasic insulin regimens, and found that both approaches are equally efficacious at lowering A1C, with comparable effects on hypoglycemia risk and weight—although basal-bolus regimens were modestly more efficacious in people with type 2 diabetes already on insulin (102). Bolus insulin should be initiated using a stepwise approach (starting with 1 injection at the largest meal and additional mealtime injections at 3-month intervals if needed), as it was shown to be as efficacious at A1C lowering as a full basal-bolus regimen, and is associated with less hypoglycemia and greater patient satisfaction after 1 year (103).

Lower rates of hypoglycemia have been observed in some studies of individuals with type 2 diabetes treated with rapid-acting insulin analogues (insulin aspart, insulin lispro, insulin glulisine) compared to those treated with short-acting (regular) insulin (104–106). Use of long-acting basal insulin analogues (insulin detemir, insulin glargine, insulin degludec) in those already on antihyperglycemic agents reduces the relative risk of symptomatic and nocturnal hypoglycemia compared to treatment with NPH insulin (83,104,107–112). Meta-analyses indicate a relative reduction of 0.89 (95% CI 0.83–0.96) and 0.63 (95% CI 0.51–0.77) for symptomatic and nocturnal hypoglycemia respectively (112); and rates of 26% vs. 34% and 13% vs. 22% for at least one symptomatic and nocturnal hypoglycemic event with an analogue vs. NPH (111). Insulin degludec has been associated with lower rates of overall and nocturnal hypoglycemia compared to glargine U-100 (82,84,113). The Randomised, Double Blind, Cross-over Trial Comparing the Safety and Efficacy of Insulin Degludec and Insulin Glargine, With or Without OADs in Subjects With Type 2 Diabetes (SWITCH 2) trial randomized patients with type 2 diabetes and at least one risk factor for hypoglycemia (history of hypoglycemia, >5 years of insulin therapy, hypoglycemia unawareness or moderate chronic renal failure) to insulin degludec or glargine U-100. After 32 weeks of treatment, insulin degludec was associated with a significantly lower rate of the primary endpoint of overall symptomatic hypoglycemic episodes (rate ratio 0.70, 95% CI 0.61–0.80). The proportions of patients with hypoglycemic episodes were 9.7% and 14.7% for insulin degludec

and glargine U-100, respectively (114). The Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) randomized patients with type 2 diabetes at high risk of CV disease to insulin degludec or glargine U-100, and found no difference in the primary outcome of CV events but a significant decrease in severe hypoglycemia with degludec (4.6%) compared to glargine U-100 (6.6%; odds ratio, 0.73; p<0.001 for superiority) (84). Insulin degludec may thus be considered over glargine U-100 in patients at high risk of hypoglycemia and/or CV disease. There is also some evidence of lower hypoglycemia rates with glargine U-300 compared to glargine U-100 (115) and may also be considered over glargine U-100 if reducing hypoglycemia is a priority (116). Efficacy and rates of hypoglycemia are similar between glargine U-100 and detemir (117).

Adverse Effects

Aside from effects of some antihyperglycemic agents on the occurrence of hypoglycemia and weight, there are adverse effects unique to each agent (Table 1). Gastrointestinal side effects are more common with metformin, alpha glucosidase inhibitors, GLP-1 receptor agonists and orlistat than with other agents. Metformin can cause diarrhea, which tends to resolve over time and is minimized with starting at a low dose and subsequent slow titration of the dosage. Extended-release metformin can also be used to improve tolerability in individuals experiencing gastrointestinal side effects with immediate-release metformin (118–121). Metformin is also associated with an approximate 2-fold increased incidence of vitamin B12 deficiency (122–124), and vitamin B12 levels should be measured periodically in people taking metformin or with signs or symptoms of deficiency (such as impaired proprioception or peripheral neuropathy). GLP-1 receptor agonists and, less commonly, DPP-4 inhibitors can cause nausea and GLP-1 receptor agonists can also cause diarrhea. A meta-analysis comparing the risk of congestive heart failure between antihyperglycemic therapies found an increased risk with TZDs and DPP-4 inhibitors (driven by higher risk with saxagliptin) (44), although another meta-analysis (125) and a large observational study of over one million participants (126) failed to find an increased risk of heart failure with DPP-4 inhibitors compared to other agents. TZDs are also associated with a 47% increased risk of fractures compared to other agents that is predominantly seen in women (127). Reports of acute pancreatitis have been noted with DPP-4 inhibitors and GLP-1 receptor agonists. A small significant increase in pancreatitis but not pancreatic cancer was seen with DPP4-inhibitors in a meta-analysis of 3 large randomized controlled trials of over 20,000 participants (128). However, a recent large Canadian observational study of over 1.5 million people did not confirm a higher risk of pancreatitis with incretin-based therapies compared to other agents (129). SGLT2 inhibitors are associated with a 3- to 4-fold increased risk of genital mycotic infections (19,69,95), as well as higher rates of urinary tract infections, volume depletion, rare acute kidney injury and rare DKA (130,131). Canagliflozin treatment is associated with an increased risk of fractures (54,132) and a twofold increased risk of amputations (54). In a retrospective analysis, empagliflozin was not associated with an increased risk of amputations in the EMPA-REG trial (133). There is evidence of a higher risk of bladder cancer with pioglitazone in some studies (47,48) but not others (134–136), and some reports of increased bladder cancer risk with dapagliflozin (137). GLP-1 receptor agonists have been shown to promote the development of pancreatic and medullary thyroid cancer in rodents, but an increased risk has not been seen in humans (138). Semaglutide was associated with a higher risk of retinopathy in SUSTAIN-6 (see above) (56). Earlier epidemiological evidence suggesting a possible link between insulin glargine and cancer has not been substantiated in review of clinical trial data for either glargine or detemir (36,139,140).

RECOMMENDATIONS

Treatment of Newly Diagnosed People with Type 2 Diabetes

1. Healthy behaviour interventions should be initiated at diagnosis [Grade B, Level 2 (2)]. Metformin may be used at the time of diagnosis, in conjunction with healthy behaviour interventions [Grade D, Consensus].

2. If glycemic targets are not achieved using healthy behaviour interventions alone within 3 months, antihyperglycemic therapy should be added to reduce the risk of microvascular complications [Grade A, Level 1A (3)]. Metformin should be chosen over other agents due to its low risk of hypoglycemia and weight gain [Grade A, Level 1A (19)], and long-term experience [Grade D, Consensus].

3. If A1C values are ≥1.5% above target at diagnosis, initiating metformin in combination with a second antihyperglycemic agent should be considered to increase the likelihood of reaching target [Grade B, Level 2 (7–9)].

4. Individuals with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) should receive insulin with or without metformin to correct the relative insulin deficiency [Grade D, Consensus].

Treatment Advancement in People with Type 2 Diabetes in Whom Glycemic Targets are Not Achieved with Existing Antihyperglycemic Medication

5. Dose adjustments to and/or addition of antihyperglycemic medications should be made in order to attain target A1C within 3 to 6 months [Grade D, Consensus].

6. If glycemic targets are not achieved with existing antihyperglycemic medication(s), other classes of agents should be added to improve glycemic control. The choice should be individualized taking into account the information in Figure 1 and Table 1 [Grade B, Level 2 (19)].

7. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR > 30 mL/min/1.73 m^2, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to reduce the risk of:
   a. Major CV events [Grade A, Level 1A (53) for empagliflozin; Grade A, Level 1A (55) for liraglutide; Grade C, Level 2 (54) for canagliflozin]
   b. Heart failure hospitalization [Grade B, Level 2 (53) for empagliflozin; Grade C, Level 2 (54) for canagliflozin]
   c. Progression of nephropathy [Grade B, Level 2 (141) for empagliflozin; Grade C, Level 3 (54) for canagliflozin].

8. In adults with type 2 diabetes without clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s), incretin agents (DPP-4 inhibitors or GLP-1 receptor agonists) and/or SGLT2 inhibitors should be considered as add-on medication over insulin secretagogues, insulin and TZDs to improve glycemic control if lower risk of hypoglycemia and/or weight gain are priorities [Grade A, Level 1A (19,23,26,62,63,74)].

9. For adults with type 2 diabetes with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss), insulin should be used [Grade D, Consensus].

10. Insulin may be used at any time in the course of type 2 diabetes [Grade D, Consensus] (see Appendix 9. Examples of Insulin Initiation and Titration in People with Type 2 Diabetes). In people not achieving glycemic targets on existing noninsulin antihyperglycemic medication(s), the addition of a once-daily basal insulin regimen should be considered over premixed insulin or bolus only regimens, if lower risk of hypoglycemia and/or weight gain are priorities [Grade B, Level 2 (101)].

11. In adults with type 2 diabetes treated with basal insulin therapy, if lower risk of hypoglycemia is a priority:
    a. Long-acting insulin analogues (insulin glargine U-100, glargine U-300, detemir, degludec) should be considered over NPH insulin to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (82,104,110–113)]

b. Insulin degludec may be considered over insulin glargine U-100 to reduce overall and nocturnal hypoglycemia [Grade B, Level 2 for patients with ≥1 risk factor for hypoglycemia (114); Grade C, Level 3 for others (113)] and severe hypoglycemia in patients at high CV risk [Grade C, Level 3 (84)]
c. Insulin glargine U-300 may be considered over insulin glargine U-100 to reduce overall and nocturnal hypoglycemia [Grade C, Level 3 (116)].

12. In adults with type 2 diabetes receiving insulin, doses should be adjusted and/or additional antihyperglycemic medication(s) (noninsulin and/or bolus insulin) should be added if glycemic targets are not achieved [Grade D, Consensus].
    a. A GLP-1 receptor agonist should be considered as add-on therapy [Grade A, Level 1A (87,97)], before initiating bolus insulin or intensifying insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared to single or multiple bolus insulin injections [Grade A, Level 1A (25,98,99)].
    b. An SGLT2 inhibitor should be considered as add-on therapy to improve glycemic control with weight loss and lower hypoglycemic risk compared to additional insulin [Grade A, Level 1A (27,93,94)].
    c. A DPP-4 inhibitor may be considered as add-on therapy to improve glycemic control without weight gain or increased hypoglycemia risk compared to additional insulin [Grade B, Level 2 (27,91)].

13. When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be used instead of short-acting (regular) insulin to improve glycemic control [Grade B, Level 2 (142)].

14. Bolus insulin may be initiated using a stepwise approach (starting with 1 injection at 1 meal and additional mealtime injections as needed) to achieve similar A1C reduction with lower hypoglycemia risk compared to initiating a full basal-bolus injection regimen [Grade B, Level 2 (103)].

15. All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the prevention, recognition and treatment of hypoglycemia [Grade D, Consensus].

16. Metformin, insulin secretagogues and SGLT2 inhibitors should be temporarily withheld during acute illnesses associated with reduced oral intake or dehydration [Grade D, Consensus]. (See Appendix 8. Sick Day Medication List.)

17. SGLT2 inhibitors should be temporarily withheld prior to major surgical procedures, and during acute infections and serious illness to reduce the risk of ketoacidosis [Grade D, Consensus].

Abbreviations
A1C, glycated hemoglobin; *BG*, blood glucose; *BP*, blood pressure; *CHF*, congestive heart failure; *CHD*, coronary heart disease; *CI*, confidence interval; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DKA*, diabetic ketoacidosis; *HR*, hazard ratio; *MI*; myocardial infarct; *NPH*, neutral protamine Hagedorn; *TZD*, thiazolidinedione.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Glycemic Management in Adults With Type 1 Diabetes, p. S80
Hypoglycemia, p. S104
Weight Management in Diabetes, p. S124
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255
Diabetes in Older People, p. S283

Relevant Appendices

Appendix 6. Types of Insulin
Appendix 7. Therapeutic Considerations for Renal Impairment
Appendix 8. Sick-Day Medication List
Appendix 9. Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

Author Disclosures

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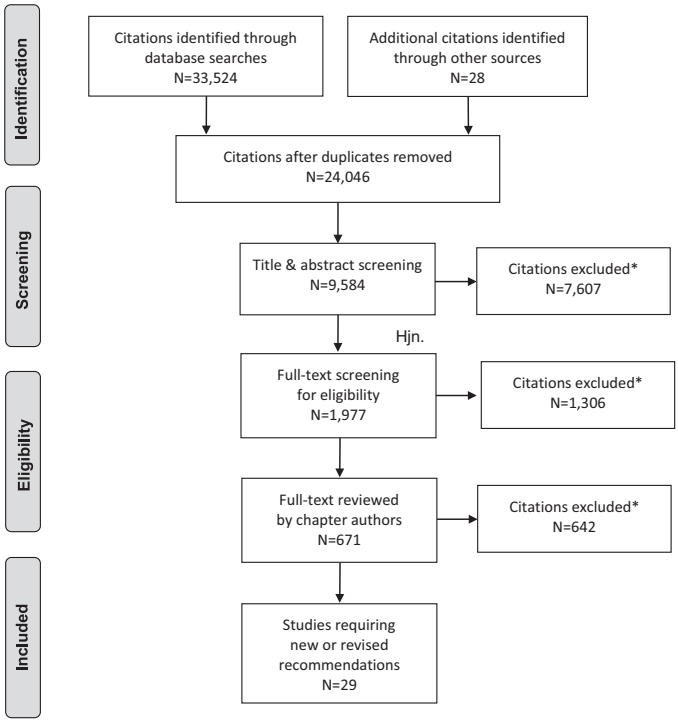
Literature Review Flow Diagram for Chapter 13: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (147).

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2018 Clinical Practice Guidelines

Hypoglycemia

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- It is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues.
- It is safer and more effective to prevent hypoglycemia than to treat it after it occurs, so people with diabetes who are at high risk for hypoglycemia should be identified and counselled about ways to prevent low blood glucose.
- It is important to counsel individuals who are at risk of hypoglycemia and their support persons about the recognition and treatment of hypoglycemia.
- The goals of treatment for hypoglycemia are to detect and treat a low blood glucose level promptly by using an intervention that provides the fastest rise in blood glucose to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. Once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is >1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed.
- It is important to avoid overtreatment of hypoglycemia, since this can result in rebound hyperglycemia and weight gain.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Know the signs and symptoms of a low blood glucose level. Some of the more common symptoms of low blood glucose are trembling, sweating, anxiety, confusion, difficulty concentrating or nausea. Not all symptoms will be present and some individuals may have other or no symptoms.
- Carry a source of fast-acting carbohydrate with you at all times, such as glucose tablets, Life Savers™ and/or a juice box (see Table 4).
- Wear diabetes identification (e.g. a MedicAlert® bracelet)
- Talk with your diabetes health-care team about prevention and emergency treatment of a severe low blood glucose associated with confusion, loss of consciousness or seizure.

Introduction

Drug-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. Frequency and severity of hypoglycemia negatively impact on quality of life (1) and promote fear of future hypoglycemia (2,3). This fear is associated with reduced self-care and poor glucose control (4–6). The negative social and emotional impact of hypoglycemia may make individuals reluctant to intensify therapy. As such, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues (see Glycemic Management in Adults with Type 1 Diabetes, p. S80; Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88 for further discussion of drug-induced hypoglycemia).

Definition and Frequency of Hypoglycemia

Hypoglycemia is defined by: 1) the development of autonomic or neuroglycopenic symptoms (Table 1); 2) a low plasma glucose (PG) level (<4.0 mmol/L for people with diabetes treated with insulin or an insulin secretagogue); and 3) symptoms responding to the administration of carbohydrate (7). The severity of hypoglycemia is defined by clinical manifestations (Table 2). Hypoglycemia is most frequent in people with type 1 diabetes, followed by people with type 2 diabetes managed by insulin, and people with type 2 diabetes managed by sulfonylureas.

Severe Hypoglycemia and Hypoglycemia Unawareness

The major risk factors for severe hypoglycemia in people with type 1 diabetes include a prior episode of severe hypoglycemia

Table 1
Symptoms of hypoglycemia

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion, weakness, drowsiness, vision changes
Sweating	Difficulty speaking, headache, dizziness
Anxiety	
Hunger	
Nausea	
Tingling	

Table 2
Severity of hypoglycemia

Mild: Autonomic symptoms are present. The individual is able to self-treat.
Moderate: Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.
Severe: Individual requires assistance of another person. Unconsciousness may occur. PG is typically <2.8 mmol/L.

PG, plasma glucose.

Conflict of interest statements can be found on page S106.

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Table 3
Risk factors for severe hypoglycemia in people treated with sulfonylureas or insulin

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of insulin therapy
- Autonomic neuropathy
- Chronic kidney disease
- Low economic status, food insecurity
- Low health literacy
- Preschool-aged children unable to detect and/or treat mild hypoglycemia on their own
- Adolescence
- Pregnancy
- Elderly
- Cognitive impairment

A1C, glycated hemoglobin.

(8–10), current low glycated hemoglobin (A1C) (<6.0%) (9,11–13), hypoglycemia unawareness (14), long duration of diabetes (12,15), autonomic neuropathy (16), adolescence (17) and preschool-aged children unable to detect and/or treat mild hypoglycemia on their own. Risk factors for hypoglycemia in people with type 2 diabetes include advancing age (18), severe cognitive impairment (19), poor health literacy (20), food insecurity (21), increased A1C (18,22), hypoglycemia unawareness (23), duration of insulin therapy, renal impairment and neuropathy (22). Individuals at high risk for severe hypoglycemia should be informed of their risk and counselled, along with their significant others, on preventing and treating hypoglycemia (including use of glucagon), preventing driving and industrial accidents through self-monitoring of blood glucose (SMBG), and taking appropriate precautions prior to the activity, and documenting blood glucose (BG) readings taken during sleeping hours. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk. Risk factors for severe hypoglycemia are listed in Table 3.

Frequent hypoglycemia can decrease normal responses to hypoglycemia (12) and lead to defective glucose counter-regulation and hypoglycemia unawareness. Hypoglycemia unawareness occurs when the threshold for the development of autonomic warning symptoms is close to, or lower than, the threshold for the neuroglycopenic symptoms, such that the first sign of hypoglycemia is confusion or loss of consciousness. Severe hypoglycemia is often the primary barrier to achieving glycemic targets in people with type 1 diabetes (24) and occurs frequently during sleep or in the presence of hypoglycemia unawareness (11,25). The sympathoadrenal response to hypoglycemia is reduced during sleep, and following exercise or alcohol consumption (26,27). Asymptomatic nocturnal hypoglycemia is common and often lasts greater than 4 hours (11,28–31). Severe hypoglycemia, resulting in seizures, is more likely to occur at night than during the day (12).

Both hypoglycemia unawareness and defective glucose counter-regulation are potentially reversible. Strict avoidance of hypoglycemia for a period of 2 days to 3 months has been associated with improvement in the recognition of severe hypoglycemia, the counter-regulatory hormone responses or both (32–39). To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using intensive insulin therapy should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin.

Structured educational and psycho-behavioural programs (e.g. BG awareness training) may help improve detection of hypoglycemia and reduce the frequency of severe hypoglycemia (40–43). People with diabetes who continue to have frequent and severe hypoglycemia and/or impaired awareness of hypoglycemia, despite educational interventions, may benefit from continuous subcutaneous insulin infusion (CSII) therapy or continuous glucose monitoring (CGM) or both (i.e. a sensor augmented pump), to reduce the risk of severe hypoglycemia (44–47). Islet cell transplantation, which has been shown to reduce hypoglycemia (48) and restore glucose counter-regulation (49), should be considered for people with type 1 diabetes who experience recurrent severe hypoglycemia (50) (see Diabetes and Transplantation chapter, p. S145). Similarly, pancreas transplantation has been shown to reduce hypoglycemia and restore glucose counter-regulation (43,51–53).

Complications of Severe Hypoglycemia

Short-term risks of hypoglycemia include the dangerous situations that can arise while an individual is hypoglycemic, whether at home or at work (e.g. driving, operating machinery).

In addition, prolonged coma is sometimes associated with transient neurological symptoms, such as paresis, convulsions and encephalopathy. The potential long-term complications of severe hypoglycemia are mild intellectual impairment and permanent neurologic sequelae, such as hemiparesis and pontine dysfunction. The latter are rare and have been reported only in case studies. Recurrent hypoglycemia may impair the individual's ability to sense subsequent hypoglycemia (54,55).

There is a clear association between severe hypoglycemia and cognitive disorders, but the nature of this relationship remains unclear. The person with cognitive disorders is at high risk of future severe hypoglycemic episodes, possibly because of medication errors (19,56,57) (see Diabetes in Older People chapter, p. S283). Prospective studies have not found an association between intensive insulin therapy and cognitive function (58–60), or between severe hypoglycemia and future cognitive function (56,57). Lowered cognitive performance appears to be more associated with the presence of microvascular complications or poor metabolic control than with the occurrence of severe hypoglycemic episodes (57,61).

In people with type 2 diabetes and established, or very high risk for, cardiovascular disease (CVD), there is a clear association between an increased mortality and severe hypoglycemia (62,63) and symptomatic hypoglycemia (64). The mechanism for this increase is not certain. Acute hypoglycemia is proinflammatory, increases platelet activation and decreases fibrinolysis, leading to a prothrombotic state (65,66). Hypoglycemia is associated with increased heart rate, systolic blood pressure (BP), myocardial contractility, stroke volume and cardiac output, and can induce ST- and T-wave changes with a lengthening of the QT interval (slower repolarization), which may increase the risk of arrhythmias (67–71). However, severe hypoglycemia may also be a marker of vulnerability, without any direct causal contribution to the increased mortality (72).

Treatment of Hypoglycemia

The goals of treatment for hypoglycemia are to detect and treat a low BG level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. It is also important to avoid overtreatment since this can result in rebound hyperglycemia and weight gain. Evidence suggests that 15 g glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people (Table 4) (73–77). This has not been well studied in individuals with gastroparesis. A 20 g oral glucose dose will produce a BG increment of approximately 3.6 mmol/L at 45 minutes (74,75). Other choices, such as milk and orange juice, are slower to increase BG levels and provide symptom relief (74,75). Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect (73–78). People taking an alpha glucosidase

Table 4
Examples of 15 g of carbohydrate for the treatment of mild-to-moderate hypoglycemia

- 15 g of glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 5 cubes of sugar
- 150 mL of juice or regular soft drink
- 6 Life Savers™ (1 = 2.5 g of carbohydrate)
- 15 mL (1 tablespoon) of honey

inhibitor (acarbose) must use glucose (dextrose) tablets (79) or, if unavailable, milk or honey to treat hypoglycemia.

Glucagon 1 mg given subcutaneously or intramuscularly produces a significant increase in BG (from 3.0 to 12.0 mmol/L) within 60 minutes (80). The effectiveness of glucagon is reduced in individuals who have consumed more than 2 standard alcoholic drinks in the previous few hours, after prolonged fasting, or in those who have advanced hepatic disease (81,82).

RECOMMENDATIONS

1. All people with diabetes currently using or starting therapy with insulin or insulin secretagogues and their support persons should be counselled about the risk, prevention, recognition and treatment of hypoglycemia. Risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].

2. The DHC team should review the person with diabetes' experience with hypoglycemia at each visit, including an estimate of cause, frequency, symptoms, recognition, severity and treatment, as well as the risk of driving with hypoglycemia [Grade D, Consensus].

3. In people with diabetes at increased risk of hypoglycemia, the following strategies may be used to reduce the risk of hypoglycemia:
   a. Avoidance of pharmacotherapies associated with increased risk of recurrent or severe hypoglycemia (see Glycemic Management in Adults with Type 1 Diabetes, p. S80; Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88, for further discussion of drug-induced hypoglycemia) [Grade D, Consensus]
   b. A standardized education program targeting rigorous avoidance of hypoglycemia while maintaining overall glycemic control [Grade B, Level 2 (83)]
   c. Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus]
   d. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade D, Level 4 (37,38)]
   e. A psycho-behavioural intervention program (blood glucose awareness training) [Grade C, Level 3 (40)]
   f. Structured diabetes education and frequent follow up [Grade C, Level 3 (42) for type 1 diabetes; Grade D, Consensus for type 2].

4. In people with diabetes with recurrent or severe hypoglycemia, or impaired awareness of hypoglycemia, the following strategies may be considered to reduce or eliminate the risk of severe hypoglycemia and to attempt to regain hypoglycemia awareness:
   a. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade D, Level 4 (37,38)]
   b. CSII or CGM or sensor augmented pump with education and follow up for type 1 diabetes [Grade B, Level 2 (42,44,46,47)]
   c. Islet transplantation for type 1 diabetes [Grade C, Level 3 (48)]
   d. Pancreas transplantation for type 1 diabetes [Grade D, Level 4 (50–53)].

5. Mild-to-moderate hypoglycemia should be treated by the oral ingestion of 15 g carbohydrate, preferably as glucose or sucrose tablets or solution. These are preferable to orange juice and glucose gels [Grade B, Level 2 (73)]. People with diabetes should retest BG in 15 minutes and re-treat with another 15 g carbohydrate if the BG level remains <4.0 mmol/L [Grade D, Consensus].
   Note: This does not apply to children. See Type 1 Diabetes in Children and Adolescents, p. S234; and Type 2 Diabetes in Children and Adolescents, p. S247, for treatment options in children.

6. Severe hypoglycemia in a conscious person with diabetes should be treated by oral ingestion of 20 g carbohydrate, preferably as glucose tablets or equivalent. BG should be retested in 15 minutes and then re-treated with another 15 g glucose if the BG level remains <4.0 mmol/L [Grade D, Consensus].

7. Severe hypoglycemia in an unconscious person with diabetes:
   a. With no intravenous access: 1 mg glucagon should be given subcutaneously or intramuscularly. Caregivers or support persons should call for emergency services and the episode should be discussed with the DHC team as soon as possible [Grade D, Consensus]
   b. With intravenous access: 10–25 g (20–50 mL of D50W) of glucose should be given intravenously over 1–3 minutes [Grade D, Consensus].

8. Once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is >1 hour away, a snack (including 15 g carbohydrate and a protein source) should be consumed [Grade D, Consensus].

9. For people with diabetes at risk of severe hypoglycemia, support persons should be taught how to administer glucagon [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *CVD*, cardiovascular disease; *CGM*, continuous glucose monitoring; *CSII*, continuous subcutaneous insulin infusion; *DHC*, diabetes health-care team; *SMBG*, self-monitoring of blood glucose.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Monitoring Glycemic Control, p. S47
Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Diabetes and Driving, p. S150
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255
Diabetes in Older People, p. S283

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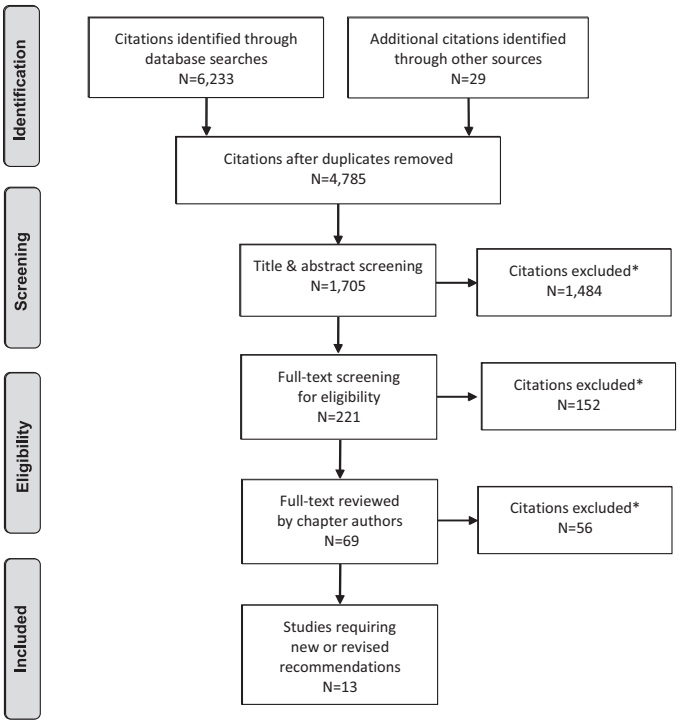
Literature Review Flow Diagram for Chapter 14: Hypoglycemia



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (84).

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2018 Clinical Practice Guidelines

Hyperglycemic Emergencies in Adults

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetic ketoacidosis and hyperosmolar hyperglycemic state should be suspected in people who have diabetes and are ill. If either diabetic ketoacidosis or hyperosmolar hyperglycemic state is diagnosed, precipitating factors must be sought and treated.
- Diabetic ketoacidosis and hyperosmolar hyperglycemic state are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.
- A normal or mildly elevated blood glucose level does not rule out diabetic ketoacidosis in certain conditions, such as pregnancy or with SGLT2 inhibitor use.
- Diabetic ketoacidosis requires intravenous insulin administration (0.1 units/kg/h) for resolution. Bicarbonate therapy may be considered only for extreme acidosis (pH ≤7.0).

KEY MESSAGES FOR PEOPLE WITH DIABETES

When you are sick, your blood glucose levels may fluctuate and be unpredictable:

- During these times, it is a good idea to check your blood glucose levels more often than usual (for example, every 2 to 4 hours).
- Drink plenty of sugar-free fluids or water.
- If you have type 1 diabetes with blood glucose levels remaining over 14 mmol/L before meals, or if you have symptoms of diabetic ketoacidosis (see Table 1), check for ketones by performing a urine ketone test or blood ketone test. Blood ketone testing is preferred over urine testing.
- Develop a sick-day plan with your diabetes health-care team. This should include information on:
  - Which diabetes medications you should continue and which ones you should temporarily stop
  - Guidelines for insulin adjustment if you are on insulin
  - Advice on when to contact your health-care provider or go to the emergency room.

Note: Although the diagnosis and treatment of diabetic ketoacidosis (DKA) in adults and in children share general principles, there are significant differences in their application, largely related to the increased risk of life-threatening cerebral edema with DKA in children and adolescents. The specific issues related to treatment of DKA in children and adolescents are addressed in the Type 1 Diabetes in Children and Adolescents chapter, p. S234.

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are diabetes emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and insulin deficiency (in the case of type 1 diabetes). There may also be high catecholamine levels suppressing insulin release (in the case of type 2 diabetes). In DKA, ketoacidosis is prominent while, in HHS, the main features are ECFV depletion and hyperosmolarity. HHS is the preferred term to describe this condition as opposed to hyperosmolar nonketotic coma (HONKC) since less than one-third of people with HHS actually present with a coma (1).

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction (MI), abdominal crisis, trauma and, possibly, continuous subcutaneous insulin infusion (CSII) therapy, thyrotoxicosis, cocaine, atypical antipsychotics and, possibly, interferon. HHS is much less common than DKA (2,3). In addition to the precipitating factors noted above for DKA, HHS also has been reported following cardiac surgery and with the use of certain drugs, including diuretics, glucocorticoids, lithium and atypical antipsychotics. Infections are present in 40% to 60% of people with HHS (4). In up to 20% of cases of HHS, individuals had no prior history of diabetes (4).

The clinical presentation of DKA includes symptoms and signs of hyperglycemia, acidosis and the precipitating illness (Table 1). In HHS, there is often more profound ECFV contraction and decreased level of consciousness (proportional to the elevation in plasma osmolality). In addition, in HHS, there can be a variety of neurological presentations, including seizures and a stroke-like state that can resolve once osmolality returns to normal (3,5,6). In HHS, there also may be evidence of a precipitating condition similar to DKA.

In individuals with type 2 diabetes, the incidence of DKA is estimated to be in the range of 0.32 to 2.0 per 1,000 patient-years (7) while, in people with type 1 diabetes, the incidence is higher at 4.6

Table 1
Clinical presentation of DKA

	Symptoms	Signs
Hyperglycemia	Polyuria, polydipsia, weakness	ECFV contraction
Acidosis	Air hunger, nausea, vomiting and abdominal pain Altered sensorium	Kussmaul respiration, acetone-odoured breath Altered sensorium
Precipitating condition	See list of conditions in Table 2	

Conflict of interest statements can be found on page S113.

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to 8.0 per 1000 patient-years (8). There is a group of individuals with diabetes that present with DKA but do not have the typical features of type 1 diabetes. There are various terms given to characterize this condition, such as flatbush diabetes, type 1.5 diabetes, atypical diabetes or type 1B diabetes, but it may be most useful to label this state as ketosis-prone diabetes (KPD). There are several classification systems used to describe KPD that take into account pathophysiology and prognosis. Individuals with KPD have very little beta cell function, may or may not have beta cell antibodies, and some may require temporary or lifelong insulin therapy (9).

Prevention

Sick-day management that includes capillary beta-hydroxybutyrate monitoring reduces emergency room visits and hospitalizations in young people (10).

SGLT2 Inhibitors and DKA

SGLT2 inhibitors may lower the threshold for developing DKA through a variety of different mechanisms (11–13). The presentation of the DKA is similar to those who develop DKA without SGLT2 inhibitor exposure, except that the blood glucose (BG) levels on presentation may not be as elevated as expected. In randomized controlled trials, the incidence of DKA associated with SGLT2 inhibitors is low (≤0.1% of treated people) (14,15). In most cases, there is usually a known precipitant as a contributing factor, such as insulin dose reduction or omission, bariatric surgery or other surgery, alcohol, exercise, or low carbohydrate or reduced food intake (16–20).

Diagnosis

DKA or HHS should be suspected whenever people have significant hyperglycemia, especially if they are ill or highly symptomatic (see above). As outlined in Figure 1, to make the diagnosis and determine the severity of DKA or HHS, the following should be assessed: plasma levels of electrolytes (and anion gap), plasma glucose (PG), creatinine, osmolality and beta-hydroxybutyric acid (beta-OHB) (if available), blood gases, serum and urine ketones, fluid balance, level of consciousness, precipitating factors and complications (1). Arterial blood gases may be required for more ill individuals, when knowing the adequacy of respiratory compensation and the A-a gradient is necessary. Otherwise, venous blood gases are usually adequate—the pH is typically 0.015 to 0.03 lower than arterial pH (21-23). Point-of-care capillary blood beta-OHB measurement in emergency is sensitive and specific for DKA and, as a screening tool, may allow more rapid identification of hyperglycemic persons at risk for DKA (24–29). This test is less accurate with hemoconcentration and/or when the beta-OHB level is >3 mmol/L (30).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is ≤7.3, serum bicarbonate is ≤15 mmol/L and the anion gap is >12 mmol/L with positive serum and/or urine ketones (1,31–33). PG is usually ≥14.0 mmol/L but can be lower, especially with the use of SGLT2 inhibitors (34). DKA is more challenging to diagnose in the presence of the following conditions: 1) mixed acid-base disorders (e.g. associated vomiting, which will raise the bicarbonate level); 2) if there has been a shift in the redox potential, favouring the presence of beta-OHB (rendering serum ketone testing negative); or 3) if the loss of keto anions with sodium or potassium in osmotic diuresis has occurred, leading to a return of the plasma anion gap toward normal. It is, therefore, important to measure ketones in both the serum and urine. If there is an elevated anion gap and serum ketones are negative, beta-OHB levels should be measured. Negative urine ketones should not be used to rule out DKA (35).

Measurement of serum lactate should be considered in hypoxic states. In HHS, a more prolonged duration of relative insulin insufficiency and inadequate fluid intake (or high glucose intake) results in higher PG levels (typically ≥34.0 mmol/L), plasma osmolality >320 mOsm/kg and greater ECFV contraction, but minimal acid-base disturbance (1,31).

Pregnant women in DKA typically present with lower PG levels than nonpregnant women (36), and there are case reports of euglycemic DKA in pregnancy (37,38).

Management

Objectives of management include restoration of normal ECFV and tissue perfusion; resolution of ketoacidosis; correction of electrolyte imbalances and hyperglycemia; and the diagnosis and treatment of coexistent illness. The issues that must be addressed in the individual presenting with DKA or HHS are outlined in Table 2. A summary of fluid therapy is outlined in Table 3, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

People with DKA and HHS are best managed in an intensive care unit or step-down setting (1,31,32) with specialist care (39,40). Protocols and insulin management software systems (41) may be beneficial (42,43), but there can be challenges with achieving adherence (44,45). Volume status (including fluid intake and output), vital signs, neurological status, plasma concentrations of electrolytes, anion gap, osmolality and glucose need to be monitored closely, initially as often as every 2 hours (1,31,32). Capillary blood glucose (CBG) measurements are unreliable in the setting of severe acidosis (46). Precipitating factors must be diagnosed and treated (1,31,32).

Table 2
Priorities* to be addressed in the management of adults presenting with hyperglycemic emergencies

Metabolic	Precipitating cause of DKA/HHS	Other complications of DKA/HHS
• ECFV contraction • Potassium deficit and abnormal concentration • Metabolic acidosis • Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia)	• New diagnosis of diabetes • Insulin omission • Infection • Myocardial infarction • Stroke • ECG changes may reflect hyperkalemia (78,79) • A small increase in troponin may occur without overt ischemia (80) • Thyrotoxicosis (81) • Trauma • Drugs	• Hyper/hypokalemia • ECFV overexpansion • Cerebral edema • Hypoglycemia • Pulmonary emboli • Aspiration • Hypocalcemia (if phosphate used) • Stroke • Acute renal failure • Deep vein thrombosis

DKA, diabetic ketoacidosis; *ECFV*, extracellular fluid volume; *HHS*, hyperosmolar hyperglycemic state.
* Severity of issue will dictate priority of action.

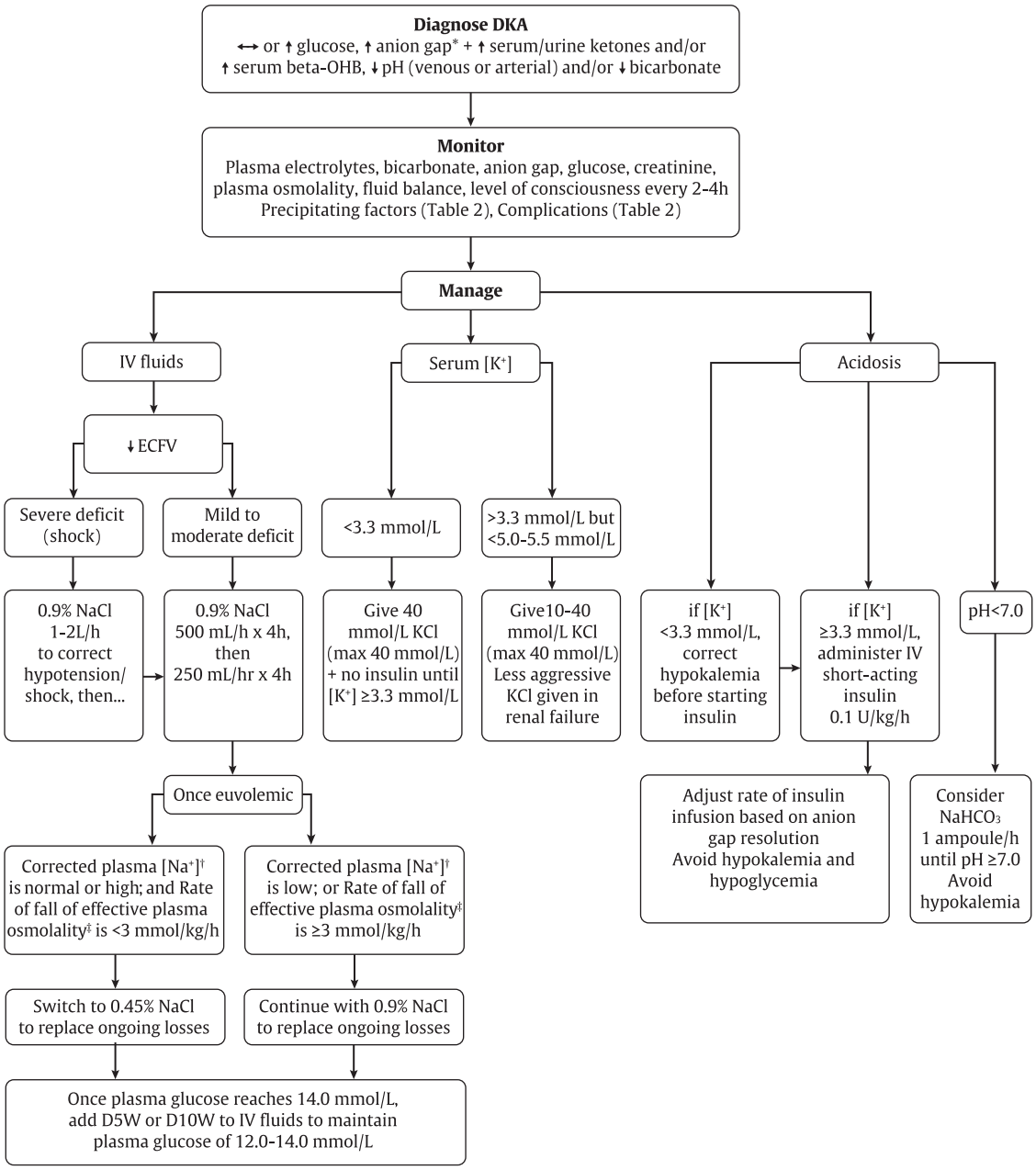

Figure 1. Management of diabetic ketoacidosis in adults.
Beta-OHB, beta-hydroxybutyric acid; *DKA*, diabetic ketoacidosis; *ECFV*, extracelluar fluid volume; *IV*, intravenous.
*Plasma glucose may be lower than expected in some settings.
**Anion gap = plasma [Na+] – plasma [Cl^-] – plasma [HCO_3^-].
†Corrected plasma [Na+] = measured [Na+] + 3/10 × ([plasma glucose (mmol/L)] – 5).
‡Effective plasma osmolality = [Na+] × 2 + [plasma glucose (mmol/L)], reported as mmol/kg.

Extracellular fluid volume contraction

The sodium deficit is typically 7 to 10 mmol/kg in DKA (47) and 5 to 13 mmol/kg in HHS, which, along with water losses (100 mL/kg and 100 to 200 mL/kg, respectively), results in decreased ECFV, usually with decreased intracellular fluid volume (47). Restoring ECFV improves tissue perfusion and reduces plasma glucose levels both by dilution and by increasing urinary glucose losses. ECFV re-expansion, using a rapid rate of initial fluid administration, was associated with an increased risk of cerebral edema in 1 study (48) but not in another (49). In adults, one should initially administer intravenous normal saline 1 to 2 L/h to correct shock, otherwise 500 mL/h for 4 hours, then 250 mL/h of intravenous fluids (50,51).

Potassium deficit

The typical potassium deficit range is 2 to 5 mmol/kg in DKA and 4 to 6 mmol/kg in HHS (48). There have been no randomized trials that have studied strategies for potassium replacement. Typical recommendations suggest that potassium supplementation should be started for plasma potassium <5.0 to 5.5 mmol/L once diuresis has been established, usually with the second litre of saline. If the individual at presentation is normo- or hypokalemic, potassium should be given immediately, at concentrations in the intravenous fluid between 10 to 40 mmol/L, at a maximum rate of 40 mmol/h.

In the case of frank hypokalemia (serum potassium <3.3 mmol/L), insulin should be withheld until potassium

Table 3
Summary of fluid therapy for DKA and HHS in adults

1. Administer IV 0.9% sodium chloride initially. If the person is in shock, give 1 to 2 L/hour initially to correct shock; otherwise, give 500 mL/hour for 4 h, then 250 mL/hour for 4 h, then as required.
2. Add potassium immediately if person is normo- or hypokalemic. Otherwise, if initially hyperkalemic, only add potassium once serum potassium falls to <5 to 5.5 mmol/L and person is diuresing.
3. Once plasma glucose reaches 14.0 mmol/L, add glucose to maintain plasma glucose at 12.0 to 14.0 mmol/L.
4. After hypotension has been corrected, switch 0.9% sodium chloride to 0.45% sodium chloride (with potassium chloride). However, if plasma osmolality is falling more rapidly than 3 mmol/kg/hour and/or the corrected plasma sodium is reduced, maintain intravenous fluids at higher osmolality (i.e. may need to maintain on normal saline).

DKA, diabetic ketoacidosis; *HHS*, hyperosmolar hyperglycemic state; *IV*, intravenous.

replacement at 40 mmol/h has restored plasma potassium to ≥3.3 mmol/L (1,31). It is reasonable to treat the potassium deficit of HHS in the same way.

Metabolic acidosis

Metabolic acidosis is a prominent component of DKA. People with HHS have minimal or no acidosis. Insulin is used to stop ketoacid production; intravenous fluid alone has no impact on parameters of ketoacidosis (52). Short-acting insulin (0.1 units/kg/h) is recommended (53–55). There is no conclusive evidence supporting the use of an initial insulin bolus in adults and it is not recommended in children. Although the use of an initial bolus of intravenous insulin is recommended in some reviews (1), there has been only 1 randomized controlled trial in adults examining the effectiveness of this step (56). In this study, there were 3 arms: a bolus arm (0.07 units/kg, then 0.07 units/kg/h), a low-dose infusion group (no bolus, 0.07 units/kg/h) and a double-dose infusion group (no bolus, 0.14 units/kg/h). Outcomes were identical in the 3 groups, except 5 of 12 participants needed extra insulin in the no-bolus/low-dose infusion group, and the double-dose group had the lowest potassium (nadir of 3.7 mmol/L on average). Unfortunately, this study did not examine the standard dose of insulin in DKA (0.1 units/kg/h). In children, using an initial bolus of intravenous insulin does not result in faster resolution of ketoacidosis (57,58) and increases the risk of cerebral edema (see Type 1 Diabetes in Children and Adolescents chapter, p. S234).

A systematic review based on low- to very-low-quality evidence, showed that subcutaneous hourly analogues provide neither advantages nor disadvantages compared to intravenous regular insulin when treating mild to moderate DKA (59). The dose of insulin should subsequently be adjusted based on ongoing acidosis (60), using the plasma anion gap or beta-OHB measurements.

Use of intravenous sodium bicarbonate to treat acidosis did not affect outcome in randomized controlled trials (61–63). Sodium bicarbonate therapy may be considered in adult individuals in shock or with arterial pH ≤7.0. For example, one can administer 1 ampoule (50 mmol) sodium bicarbonate added to 200 mL D5W (or sterile water, if available) over 1 hour, repeated every 1 to 2 hours, until pH is ≥7.0 (1,31). Potential risks associated with the use of sodium bicarbonate include hypokalemia (64) and delayed occurrence of metabolic alkalosis.

Hyperosmolality

Hyperosmolality is due to hyperglycemia and a water deficit. However, serum sodium concentration may be reduced due to shift of water out of cells. The concentration of sodium needs to be corrected for the level of glycemia to determine if there is also a water deficit (Figure 1). In people with DKA, plasma osmolality is usually ≤320 mmol/kg. In HHS, plasma osmolality is typically >320 mmol/kg. Because of the risk of cerebral edema with rapid reductions in osmolality (65), it has been recommended that the plasma osmolality be lowered no faster than 3 mmol/kg/h (1,31). This can be achieved by monitoring plasma osmolality, by adding glucose to the infusions when PG reaches 14.0 mmol/L to maintain it at that level and by selecting the correct concentration of intravenous saline. Typically, after volume re-expansion, intravenous fluid may be switched to half-normal saline because urinary losses of electrolytes in the setting of osmotic diuresis are usually hypotonic. The potassium in the infusion will also add to the osmolality. If osmolality falls too rapidly despite the administration of glucose, consideration should be given to increasing the sodium concentration of the infusing solution (1,31). Water imbalances can also be monitored using the corrected plasma sodium. Central pontine myelinolysis has been reported in association with overly rapid correction of hyponatremia in HHS (66).

PG levels will fall due to multiple mechanisms, including ECFV re-expansion (67), glucose losses via osmotic diuresis (52), insulin-mediated reduced glucose production and increased cellular uptake of glucose. Once PG reaches 14.0 mmol/L, intravenous glucose should be started to prevent hypoglycemia, targeting a plasma glucose of 12.0 to 14.0 mmol/L. Similar doses of intravenous insulin can be used to treat HHS, although these individuals are not acidemic, and the fall in PG concentration is predominantly due to re-expansion of ECFV and osmotic diuresis (67). Insulin has been withheld successfully in HHS (68), but generally its use is recommended to reduce PG levels (1,31).

Phosphate deficiency

There is currently no evidence to support the use of phosphate therapy for DKA (69–71), and there is no evidence that hypophosphatemia causes rhabdomyolysis in DKA (72). However, because hypophosphatemia has been associated with rhabdomyolysis in other states, administration of potassium phosphate in cases of severe hypophosphatemia may be considered for the purpose of trying to prevent rhabdomyolysis.

Complications

In Ontario, in-hospital mortality in people hospitalized for acute hyperglycemia ranged from <1% at ages 20 to 49 years to 16% in those over 75 years (73). Reported mortality in DKA ranges from 0.65% to 3.3% (3,39,74–76). In HHS, recent studies found mortality rates to be 12% to 17%, but included individuals with mixed DKA and hyperosmolality (2,5,77). About 50% of deaths occur in the first 48 to 72 hours. Mortality is usually due to the precipitating cause, electrolyte imbalances (especially hypo- and hyperkalemia) and cerebral edema.

RECOMMENDATIONS

1. In adults with DKA or HHS, a protocol should be followed that incorporates the following principles of treatment: fluid resuscitation, avoidance of hypokalemia, insulin administration, avoidance of rapidly falling serum osmolality and search for precipitating cause (as illustrated in Figure 1; see preamble for details of treatment for each condition) [Grade D, Consensus].

2. Point-of-care capillary beta-hydroxybutyrate may be measured in the hospital or outpatient setting [Grade D, Level 4 (33)] in adults with type 1 diabetes with CBG >14.0 mmol/L to screen for DKA, and a beta-hydroxybutyrate >1.5 mmol/L warrants further testing for DKA [Grade B, Level 2 (24–29)]. Negative urine ketones should not be used to rule out DKA [Grade D, Level 4 (35)].

3. In adults with DKA, intravenous 0.9% sodium chloride should be administered initially at 500 mL/h for 4 hours, then 250 mL/h for 4 hours [Grade B, Level 2 (50)] with consideration of a higher initial rate (1–2 L/h) in the presence of shock [Grade D, Consensus]. For adults with HHS, intravenous fluid administration should be individualized [Grade D, Consensus].

4. In adults with DKA, an infusion of short-acting intravenous insulin of 0.10 units/kg/h should be used [Grade B, Level 2 (54,55)]. The insulin infusion rate should be maintained until the resolution of ketosis [Grade B, Level 2 (60)] as measured by the normalization of the plasma anion gap [Grade D, Consensus]. Once the PG concentration falls to 14.0 mmol/L, intravenous dextrose should be started to avoid hypoglycemia [Grade D, Consensus].

5. Individuals treated with SGLT2 inhibitors with symptoms of DKA should be assessed for this condition even if BG is not elevated [Grade D, Consensus].

Abbreviations:
BG, blood glucose; *CBG*, capillary blood glucose; *DKA*, diabetic ketoacidosis; *ECFV*, extracellular fluid volume; *HHS*, hyperosmolar hyperglycemic state; *KPD*, ketosis-prone diabetes, *PG*, plasma glucose.

Other Relevant Guidelines

Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Type 1 Diabetes in Children and Adolescents, p. S234

Relevant Appendix

Appendix 8: Sick-Day Medication List

Author Disclosures

Dr. Gilbert reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi, outside the submitted work. Dr. Goguen does not have anything to disclose.

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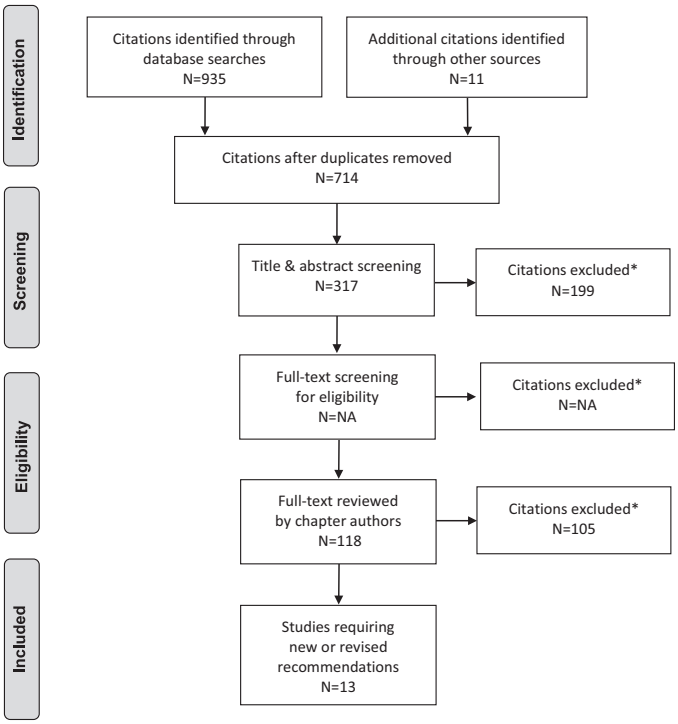
Literature Review Flow Diagram for Chapter 15: Hyperglycemic Emergencies in Adults



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

In-Hospital Management of Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Hyperglycemia is common in hospitalized people, even among those without a previous history of diabetes, and is associated with increased in-hospital complications, longer length of stay and mortality.
- Insulin is the most appropriate pharmacologic agent for effectively controlling glycemia in hospital. A proactive approach to glycemic management using scheduled basal, bolus and correction (supplemental) insulin is the preferred method. The use of correction-only (supplemental) insulin, which treats hyperglycemia only after it has occurred, should be discouraged as the sole modality for treating elevated blood glucose levels.
- For the majority of noncritically ill hospitalized people with diabetes, preprandial blood glucose targets should be 5.0 to 8.0 mmol/L, in conjunction with random blood glucose values <10.0 mmol/L, as long as these targets can be safely achieved. For critically ill hospitalized people with diabetes, blood glucose levels should be maintained between 6.0 and 10.0 mmol/L.
- Hypoglycemia is a major barrier to achieving targeted glycemic control in the hospital setting. Health-care institutions should develop protocols for the assessment and treatment of hypoglycemia.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- If your admission to hospital is planned, talk with your health-care providers (e.g. surgeon, anesthetist, primary care provider, diabetes health provider, etc.) before you are admitted in order to develop an in-hospital diabetes care plan that addresses such issues as:
  - Who will manage your diabetes in the hospital?
  - Will you be able to self-manage your diabetes?
  - What adjustments to your diabetes medications or insulin doses may be necessary before and after medical procedures or surgery?
  - If you use an insulin pump, are hospital staff familiar with pump therapy?
- Your blood glucose levels may be higher in hospital than your usual target range due to a variety of factors, including the stress of your illness, medications, medical procedures and infections.
- Your diabetes medications may need to be changed during your hospital stay to manage the changes in blood glucose, or if medical conditions develop that make some medications no longer safe to use.
- When you are discharged, make sure that you have written instructions about:
  - Changes in your dosage of medications or insulin injections or any new medications or treatments
  - How often to check your blood glucose
  - Who to contact if you have difficulty managing your blood glucose levels.

Introduction

Diabetes increases the risk for hospitalization for several reasons, including: cardiovascular (CV) disease, nephropathy, infection, cancer and lower-extremity amputations. In-hospital hyperglycemia is common. A review of medical records of over 2,000 adult patients admitted to a community teaching hospital in the United States (>85% were nonintensive care unit patients) found that hyperglycemia was present in 38% of patients (1). Of these patients, 26% had a known history of diabetes, and 12% had no history of diabetes prior to admission. Diabetes has been reported to be the fourth most common comorbid condition listed on all hospital discharges (2).

Acute illness results in a number of physiological changes (e.g. increases in circulating concentrations of stress hormones) or therapeutic choices (e.g. glucocorticoid use) that can exacerbate hyperglycemia. Hyperglycemia, in turn, causes physiological changes that can exacerbate acute illness, such as decreased immune function and increased oxidative stress. These lead to a complex cycle of worsening illness and poor glucose control (3). Although a growing body of literature supports the need for targeted glycemic control in the hospital setting, blood glucose (BG) continues to be poorly controlled and is frequently overlooked in general medicine and surgery services. This is largely explained by the fact that the majority of hospitalizations for patients with diabetes are not directly related to their metabolic state, thus diabetes management is rarely the primary focus of care. Therefore, glycemic control and other diabetes care issues are often not specifically addressed (4).

Screening for and Diagnosis of Diabetes and Hyperglycemia in the Hospital Setting

A history of diabetes should be elicited in all patients admitted to hospital and, if present, should be clearly identified on the medical record. In view of the high prevalence of inpatient hyperglycemia with associated poor outcomes, an admission BG measurement of all patients would help identify people with diabetes, even in the absence of a prior diagnosis (1,5). In-hospital hyperglycemia is defined as any glucose value >7.8 mmol/L. For hospitalized people with known diabetes, the glycated hemoglobin (A1C) identifies people who may benefit from efforts to improve glycemic control and tailor therapy upon discharge (6,7). In hospitalized people with newly recognized hyperglycemia, an A1C among those with diabetes risk factors or associated comorbidities (e.g. cardiovascular disease

Conflict of interest statements can be found on page S121.

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[CVD]) (8,9) may help differentiate people with previously undiagnosed diabetes and dysglycemia from those with stress-induced hyperglycemia and provides an opportunity to diagnose and initiate diabetes therapies (10–13). Among people admitted to an intensive care unit (ICU), an A1C drawn at admission allows identification of people with previously unknown diabetes, people at risk of glycemic management challenges and people at an increased risk of mortality (14,15). A1C has been found to be specific for diagnosis of diabetes in the hospital setting, although not as sensitive as in the outpatient setting (13,16). While the threshold for diagnosis of diabetes has not been established for hospitalized people, an A1C criteria of >6.0% has been found to be highly specific for the diagnosis of dysglycemia post-hospitalization (13,17).

Glucose Monitoring in the Hospital Setting

Bedside blood glucose monitoring

Currently, there are no studies that have examined the effect of the frequency of bedside BG monitoring on the incidence of hyper- or hypoglycemia in the hospital setting. The frequency and timing of bedside BG monitoring can be individualized; however, monitoring is typically performed before meals and at bedtime in people who are eating; every 4 to 6 hours in people who are NPO (nothing by mouth) or receiving continuous enteral feeding; and every 1 to 2 hours for people on continuous intravenous insulin or those who are critically ill. Some bedside BG monitoring is indicated in individuals without known diabetes but receiving treatments known to be associated with hyperglycemia (e.g. glucocorticoids, octreotide, parenteral nutrition and enteral nutrition) (18). The implementation and maintenance of quality control programs by health-care institutions helps to ensure the accuracy of bedside BG monitoring (19,20). The use of glucose meters with bar coding capability has been shown to reduce data entry errors in medical records (21). Data management programs that transfer bedside BG monitoring results into electronic records allow evaluation of hospital-wide glycemic control (22).

Capillary blood glucose (CBG) point of care testing (POCT) should be interpreted with caution in the critically ill patient population. Poor perfusion indices may yield conflicting capillary, arterial and whole BG values using POCT glucose meters (23–25). Venous or arterial samples are preferred when using a POCT meter for this patient population.

Clinical decision support system software integrating CBG POCT can aid in trend analysis, medication dosing, reduce prescription error and reduce length of stay (26). Electronic glucose metric data and web-based reporting systems may pose utility for monitoring glycemic management performance within an organization and enhance opportunities for external benchmarking (27).

Glycemic Control in the Non-Critically Ill Patient

A number of studies have demonstrated that inpatient hyperglycemia is associated with increased morbidity and mortality in noncritically ill hospitalized people (1,28,29). However, due to a paucity of randomized controlled trials on the benefits and risks of "conventional" vs. "tight" glycemic control in noncritically ill hospitalized people, glycemic targets for this population remain undefined. Current recommendations are based mostly on retrospective studies, clinical experience and judgement. Glycemic targets for hospitalized people with diabetes are modestly higher than those routinely advised for outpatients with diabetes given that the hospital setting presents unique challenges for the management of hyperglycemia, such as variations in patient nutritional status and the presence of acute illness. For the majority of noncritically ill hospitalized people, recommended preprandial BG targets are 5.0 to 8.0 mmol/L, in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved (Table 1). Lower targets may be considered in clinically stable hospitalized people with a prior history of successful tight glycemic control in the outpatient setting, while higher targets may be acceptable in terminally ill people or in those with severe comorbidities. If BG values are ≤3.9 mmol/L, modification of antihyperglycemic therapy is suggested, unless the event is easily explained by other factors (e.g. a missed meal) (18,30).

Table 1
Recommended glycemic targets for hospitalized people with diabetes*

Hospitalized population with diabetes	Blood glucose targets (mmol/L)
Noncritically ill	Preprandial: 5.0–8.0 Random: <10.0
Critically ill	6.0–10.0
CABG intraoperatively	5.5–11.1
Perioperatively for other surgeries	5.0–10.0
Acute coronary syndrome†	7.0–10.0
Labour and delivery‡	4.0–7.0

CABG, coronary artery bypass grafting.
* Less stringent targets may be appropriate in terminally ill patients or in people with severe comorbidities (see Targets for Glycemic Control chapter, p. S42).
† See Management of Acute Coronary Syndromes chapter, p. S190.
‡ See Diabetes and Pregnancy chapter, p. S255.

Glycemic Control in the Critically Ill Patient

Acute hyperglycemia in the intensive care setting is not unusual and results from a number of factors, including stress-induced counter-regulatory hormone secretion and the effects of medications administered in the ICU (31). Glycemic targets for people with pre-existing diabetes who are in the critical care setting have not been firmly established. Early trials showed that achieving normoglycemia (4.4 to 6.1 mmol/L) in cardiac surgery patients or patients in postoperative surgical ICU settings reduced mortality (32). However, subsequent trials in mixed populations of critically ill patients did not show a benefit of targeting BG levels of 4.4 to 8.3 mmol/L. A meta-analysis of trials of intensive insulin therapy in the ICU setting suggested benefit of intensive insulin therapy in surgical patients, but not in medical patients (33). Conversely, the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, the largest trial to date of intensive glucose control in critically ill medical and surgical patients, found an increase in 90-day all-cause mortality (hazard ratio [HR] 1.14; 95% confidence interval [CI] 1.02–1.28; p=0.02) amongst participants randomized to the intensive glycemic control arm that targeted BG levels of 4.5 to 6.0 mmol/L (34). Furthermore, intensive insulin therapy has been associated with an increased risk of hypoglycemia in the ICU setting (33). Therefore, maintaining a BG level <10.0 mmol/L in critically ill hospitalized people with diabetes is considered a safe target (Table 1). The lower limit for the BG target is less well established but generally should remain >6.0 mmol/L in order to minimize the risks of both hypoglycemia and mortality. The use of insulin infusion protocols with proven efficacy and safety minimizes the risk of hypoglycemia (35–38).

Role of Intravenous Insulin

There are few occasions when intravenous insulin is required, as most people with type 1 or type 2 diabetes admitted to general

medical wards can be treated with subcutaneous insulin. Intravenous insulin, however, may be appropriate for people who are critically ill (with appropriate BG targets), people who are not eating and in those with hyperglycemia and metabolic decompensation (e.g. diabetic ketoacidosis [DKA] and hyperosmolar hyperglycemic state [HHS]) (see Hyperglycemic Emergencies in Adults chapter, p. S109). The evidence to date suggests there is no benefit to intravenous insulin over subcutaneous insulin post-acute stroke (3,39).

Health-care staff education is a critical component of the implementation of an intravenous insulin infusion protocol. Intravenous insulin protocols should take into account the patient's current and previous BG levels (as well as the rate of change in BG), and the patient's usual insulin dose. Several published insulin infusion protocols appear to be both safe and effective, with low rates of hypoglycemia; however, most of these protocols have only been validated in the ICU setting, where the nurse-to-patient ratio is higher than on medical and surgical wards (3,36). BG determinations can be performed every 1 to 2 hours until BG has stabilized. With the exception of the treatment of hyperglycemic emergencies (e.g. DKA and HHS), consideration should be given to concurrently providing people receiving intravenous insulin with some form of glucose (e.g. intravenous glucose or through parenteral or enteral feeding).

Transition from IV insulin to SC insulin therapy

Hospitalized people with type 1 and type 2 diabetes may be transitioned to scheduled subcutaneous insulin therapy from intravenous insulin. Short- or rapid- or fast-acting insulin can be administered 1 to 2 hours before discontinuation of the intravenous insulin to maintain effective blood levels of insulin. If intermediate- or long-acting insulin is used, it can be given 2 to 3 hours prior to intravenous insulin discontinuation. People without a history of diabetes, who have hyperglycemia requiring more than 2 units of intravenous insulin per hour, likely require insulin therapy and can be considered for transition to scheduled subcutaneous insulin therapy.

The initial dose and distribution of subcutaneous insulin at the time of transition can be determined by extrapolating the intravenous insulin requirement over the preceding 6- to 8-hour period to a 24-hour period. Administering 60% to 80% of the total daily calculated dose as basal insulin has been demonstrated to be safe and efficacious in surgical patients (40). Dividing the total daily dose as a combination of basal and bolus insulin has been demonstrated to be safe and efficacious in medically ill patients (40,41).

Perioperative glycemic control

The management of individuals with diabetes at the time of surgery poses a number of challenges. Acute hyperglycemia is common secondary to the physiological stress associated with surgery. Pre-existing diabetes-related complications and comorbidities may also influence clinical outcomes. Acute hyperglycemia has been shown to adversely affect immune function (42) and wound healing (43) in animal models. Observational studies have shown that hyperglycemia increases the risk of postoperative infections (44,45), renal allograft rejection (46), and is associated with increased health-care resource utilization (47).

Cardiovascular surgery

In people undergoing coronary artery bypass grafting (CABG), a pre-existing diagnosis of diabetes has been identified as a risk factor for postoperative sternal wound infections, delirium, renal dysfunction, respiratory insufficiency and prolonged hospital stays (48–50). Intraoperative hyperglycemia during cardiopulmonary bypass has been associated with increased morbidity and mortality rates in individuals with and without diabetes (51–53). A systematic review of randomized controlled trials supports the use of intravenous insulin infusion targeting a blood glucose of 5.5 to 11.1 mmol/L over correction (supplemental) subcutaneous insulin for perioperative glycemic control in CV surgery patients (Table 1). This was demonstrated by a marked reduction in surgical site infections (odds ratio 0.13) (54).

Minor and moderate surgery

The perioperative glycemic targets for minor or moderate surgeries are less clear. Older studies comparing different methods of achieving glycemic control during minor and moderate surgeries did not demonstrate any adverse effects of maintaining perioperative BG levels between 5.0 to 11.0 mmol/L (55–57). Attention has been placed on the relationship between postoperative hyperglycemia and surgical site infections. While the association was well documented, the impact and risks of intensive management was less clear. A recent meta-analysis of 15 randomized controlled trials demonstrated that intensive perioperative glycemic control (BG target of <8.3 mmol/L) resulted in decreased odds of surgical site infections when compared to conventional control (BG target of <12 mmol/L). The risk of hypoglycemia was increased but there was no increased risk of stroke or death. The included studies looked at the intraoperative and immediate postoperative period and used intravenous insulin to achieve intensive targets. The included studies were mostly cardiac and gastrointestinal and were found to have a moderate risk of bias (58).

Rapid institution of perioperative glucose control must be carefully considered in patients with poorly controlled type 2 diabetes undergoing monocular phacoemulsification cataract surgery with moderate to severe nonproliferative diabetic retinopathy because of the possible increased risk of postoperative progression of retinopathy and maculopathy (59). The outcome of vitrectomy, however, does not appear to be influenced by perioperative control (60).

Given the data supporting tighter perioperative glycemic control during major surgeries and the compelling data showing the adverse effects of hyperglycemia, it is reasonable to target glycemic levels between 5.0 to 10.0 mmol/L for minor and moderate surgeries in patients with known diabetes (Table 1). The best way to achieve these targets in the postoperative patient is with a basal bolus insulin regimen (61,62). This approach has been shown to reduce postoperative complications, including wound infections. Despite this knowledge, surgical patients are often treated with correction (supplemental) rapid-acting insulin alone (63) which may not adequately control BG.

The benefits of improved perioperative glycemic control must be weighed against the risk of perioperative hypoglycemia. Anesthetic agents and postoperative analgesia may alter the patient's level of consciousness and awareness of hypoglycemia. The risk of hypoglycemia can be reduced by frequent BG monitoring and carefully designed management protocols.

Role of Subcutaneous Insulin

In general, insulin is the preferred treatment for hyperglycemia in hospitalized people with diabetes (35). People with type 1 diabetes must be maintained on insulin therapy at all times to prevent DKA. Scheduled subcutaneous insulin administration that consists of basal, bolus (prandial) and correction (supplemental) insulin components is the preferred method for achieving and maintaining glucose control in noncritically ill hospitalized people with diabetes or stress hyperglycemia who are eating (35,64). Bolus insulin can be withheld or reduced in people who are not eating regularly; however, basal insulin should not be withheld. Stable people

can usually be maintained on their home insulin regimen with adjustments made to accommodate for differences in meals and activity levels, the effects of illness and the effects of other medications. In the hospital setting, rapid-acting insulin analogues are the preferred subcutaneous bolus and correction insulins (65). Insulin programs that only react to, or correct for, hyperglycemia have been demonstrated to be associated with higher rates of hyperglycemia (61,66–69). Insulin is often required temporarily in hospital, even in people with type 2 diabetes not previously treated with insulin. In these insulin-naive people, there is evidence demonstrating the superiority of basal-bolus-correction insulin regimens (61,66).

A number of protocols have been published as part of studies (61,66,69–72). These studies have typically started insulin-naive people on 0.4 to 0.5 units of insulin per kilogram of body weight per day, with 40% to 50% of the total daily dose (TDD) given as basal insulin (detemir, glargine, neutral protamine Hagedorn [NPH]) and the balance given as bolus (rapid- or short-acting) insulin divided equally before each meal (i.e. breakfast, lunch and dinner); correction doses of the bolus insulin are provided if BG values are above target. Daily review of the person's BG measurements and modification of insulin doses, as required, facilitates the achievement of target blood glucose measurements.

When comparing effective protocols, the following was observed. One study compared basal-bolus (plus correction) insulin with glargine and glulisine vs. premixed insulin (30/70) (73). The study, although small (a total of 72 patients), had to be stopped early because of a tripling of the rate of hypoglycemia, BG <3.8 mmol/L, in the premixed insulin group. Average BG levels were not different, but rates of hypoglycemia were. Another study (74) found no difference in BG levels or rates of hypoglycemia when comparing insulin glargine vs. detemir, when used as the basal insulin in a basal-bolus program. Yet another study (71) found that using a weight-based algorithm to titrate insulin glargine resulted in obtaining target BG levels faster than a glucose-based algorithm, with no difference in the rates of hypoglycemia.

More recently, a study compared a basal-bolus (plus correction) insulin regimen with a program that was basal plus correction (69). The basal-bolus group had slightly lower BG through the day, which was not statistically significant, with no difference in FBG or in rates of hypoglycemia. Taken together with the earlier studies from this group (61,66), it would appear that successful management of in-hospital diabetes requires early and aggressive administration of basal insulin combined with bolus insulin, typically in the form of rapid-acting insulin analogue, similar to the approach used in the outpatient setting.

Role of Noninsulin Antihyperglycemic Agents

To date, no large studies have investigated the use of noninsulin antihyperglycemic agents on outcomes in hospitalized people with diabetes. There are often short- and/or long-term contraindications to the use of noninsulin antihyperglycemic agents in the hospital setting, such as irregular eating, acute or chronic renal failure, and exposure to intravenous contrast dye (75). Stable hospitalized people with diabetes without these contraindications can often have their home antihyperglycemic medications continued while in the hospital. However, if contraindications develop or if glycemic control is inadequate, these drugs should be discontinued and consideration given to starting the patient on a basal-bolus-supplemental insulin regimen. The advantages and disadvantages of various noninsulin antihyperglycemic therapies in hospital are discussed in detail in a recent review article (76).

A recent randomized but unblinded study compared sitagliptin plus basal (and correctional) insulin with a more traditional basal-bolus-correctional insulin program in hospitalized people with diabetes (77). The glycemic outcomes were similar between the 2 groups; however, the basal-bolus-correctional group had a higher mean glucose than similarly insulin-treated subjects in other studies (61,66). This less-aggressive treatment may explain the lack of difference between the sitagliptin and the bolus insulin groups.

Role of Medical Nutrition Therapy

Medical nutrition therapy including nutritional assessment and individualized meal planning is an essential component of inpatient glycemic management programs. A consistent carbohydrate meal planning system may facilitate glycemic control in hospitalized people and facilitate matching prandial insulin doses to the amount of carbohydrate consumed (61,66,75,78–80).

Special Clinical Situations

Hospitalized people with diabetes receiving enteral or parenteral feedings

In hospitalized people with diabetes receiving parenteral nutrition, insulin can be administered in the following ways: as scheduled regular insulin dosing added directly to the parenteral solution; or as scheduled intermediate- or long-acting subcutaneous insulin doses (81). A separate intravenous infusion of regular insulin may be an alternative method to achieve glycemic control in critical care (82). For scheduled subcutaneous insulin dosing or regular insulin added directly to parenteral solutions, the selected starting insulin dose may be based on the current estimated TDD of insulin, the composition of the parenteral nutrition solution and the patient's weight (81). Considering the patient's individual clinical situation is important when determining insulin dosing. Subcutaneous correction (supplemental) insulin may be used in addition to scheduled insulin dosing and dose adjustments made to scheduled insulin should be adjusted based on the BG pattern.

For hospitalized people with diabetes on enteral feeding regimens, there are few prospective studies examining insulin management. In 1 randomized controlled trial, low-dose basal glargine insulin with regular insulin correction dosing was compared against regular insulin correction (supplemental) insulin dosing with the addition of NPH in the presence of persistent hyperglycemia and demonstrated similar efficacy for glycemic control (83). The type of feed solution and duration of feed (cyclical vs. continuous) should be considered. People with diabetes receiving bolus enteral feeds may be treated in the same manner as people who are eating meals. Approximately 50% of the TDD can be provided as basal insulin and 50% as bolus insulin, which is administered in divided doses to match feed times (75). Correction (supplemental) insulin can be administered, as needed; added to the same bolus insulin. An insulin with a shorter half-life, such as NPH, may be preferred for intermediate duration feeding schedules (i.e. overnight), while regular or rapid-acting insulin may be more appropriate to manage hyperglycemia induced by bolus feeding schedules.

In the event that the parenteral or enteral nutrition is unexpectedly interrupted, intravenous dextrose may be required to prevent hypoglycemia depending on the last dose and type of insulin administered. When parenteral or enteral feeding schedules are adjusted in terms of carbohydrate content or duration, the insulin type and dose will need to be re-assessed.

Hospitalized people with diabetes receiving corticosteroid therapy

Hyperglycemia is a common complication of corticosteroid therapy, with a prevalence between 20% and 50% among people

without a previous history of diabetes (84). Although the optimal management of hyperglycemia in people receiving high-dose oral corticosteroids has not been clearly defined, glycemic monitoring for 48 hours after initiation of steroids may be considered for people with or without a history of diabetes (35,84). For management of hyperglycemia, treatment with a basal-bolus with correction insulin regimen was more effective and safer than a correction (supplemental) insulin-only regimen (85), although addition of NPH (dosed variably from once a day at time of glucocorticoid administration to every 6 hours depending on glucocorticoid used) was not demonstrated to improve glycemic outcomes (86,87).

Self-management of diabetes in hospital

Although data for self-management in the hospitalized setting is limited, self-management in hospital may be appropriate for people who are mentally competent and desire more autonomy over their diabetes. The majority of evidence pertains to continuous subcutaneous insulin infusion (CSII) therapy, where continuation of patient-managed insulin delivery has been associated with reduced episodes of severe hyperglycemia and hypoglycemia (88) and high levels of patient satisfaction (89). In general, any person requiring insulin therapy who is self-managing diabetes in the hospital setting should be able to physically self-administer insulin and perform self-monitoring of blood glucose (SMBG) independently, be familiar with the recommended insulin routine, understand sick-day management guidelines and utilize a flowsheet to facilitate communication of BG results and insulin dosing between the patient and health-care providers. The person with diabetes and the health-care provider, in consultation with nursing staff, must agree that patient self-management is an appropriate strategy while hospitalized. Hospitals should have policies and procedures for the assessment of suitability for self-management.

Hospitalized people with diabetes using CSII

Although the data are limited, it appears that CSII can be safely continued in the hospital setting under certain circumstances (90). People maintained on CSII may have decreased length of stay (90); however, this may reflect the severity of illness rather than a glycemic control advantage. People maintained on CSII may have less hypoglycemia than those managed by the admitting clinician. People on CSII are encouraged to continue this form of therapy whenever safe and feasible in hospital. Successful published inpatient protocols include assessment of pump specific self-management skills (i.e. how to adjust their basal rate, administer a bolus dose, insert an infusion set, fill a reservoir, suspend the pump and correct a CBG result outside their target range), pre-printed orders, flow sheets and patient consents (88,91,92). If the patient cannot demonstrate and/or describe the above-mentioned actions and desires to continue CSII, appropriate education and supports can be provided. If appropriate supports are not available, CSII may be discontinued and a basal-bolus-subcutaneous insulin regimen or intravenous insulin infusion may be initiated.

An increasing number of people are being maintained on CSII during short elective surgical procedures without any reported adverse events (93), necessitating close collaboration between anesthesia and diabetes management teams. Different pump manufacturers will recommend discontinuing pumps for certain hospital-based procedures (e.g. radiology, cautery, external beam radiation). To promote a collaborative relationship between the hospital staff and the patient, and to ensure patient safety, hospitals must have clear policies and procedures in place to guide the use of CSII in the inpatient setting (92). Documents that stipulate contraindications for continued CSII, procedures to guide medical management of CSII and a consent form outlining the inpatient terms of use (92) support the safe use of CSII use in hospital. Specific algorithms and order sets for management of CSII peri-operatively and during labour and delivery have been published (93,94).

Organization of Care

Institution-wide programs to improve glycemic control in the inpatient setting include the formation of a multidisciplinary steering committee, professional development programs focused on inpatient diabetes management (95,96), policies to assess and monitor the quality of glycemic management, interprofessional team-based care (including comprehensive patient education and discharge planning) as well as standardized order sets, protocols and algorithms for diabetes care within the institution. Implementation of such a program can result in improvements in in-hospital glycemic control (97,98).

Algorithms, order sets and decision support

Order sets for basal-bolus-correction insulin regimens, insulin management algorithms (70,96,99–102), and computerized order entry systems (101,103) have been shown to improve glycemic control and/or reduce adverse outcomes in hospitalized people with diabetes. Computerized and mobile decision support systems (that provide suggestions for insulin dosing) have also been used and have been associated with lower mean BG levels (26,104–106); hypoglycemia can be an unintended consequence of tighter glycemic control (70,105).

Interprofessional team-based approach

The timely consultation of glycemic management teams has also been found to improve the quality of care provided, reduce the length of hospital stay and lower costs (107,108), although differences in glycemic control were minimal (109). Deployment of nurses (110,111), nurse practitioners and physician assistants (112) with specialty training has been associated with greater use of basal-bolus insulin therapy and lower mean BG levels. A provincial survey of over 2,000 people with diabetes admitted to hospital found that people were more likely to be satisfied with their diabetes care in hospital if they had confidence that the team was knowledgeable about diabetes, presented a consistent message and acknowledged them in their diabetes care (113).

Comprehensive patient education

Programs that include self-management education, such as assessment of barriers and goal setting, have also been associated with improvements in glycemic control (97,111).

Metrics for evaluating inpatient glycemic management programs

Institutional implementation of hospital glycemic management programs require metrics to monitor progress, assess safety, length of stay and identify opportunities for improvement (27). Implementation of inpatient hyperglycemia quality improvement programs evaluated with real-time metrics have been shown to improve glycemic control and safety of insulin ordering (97,114). To date, metrics for monitoring glycemic control programs in hospitals have not been established (115). This lack of standardization limits the ability for benchmarking and comparison of different quality-improvement programs and protocols. Further study into the development and implementation of appropriate

standardized metrics for hospital glycemic management programs is warranted.

Transition from hospital to home

Interventions that ensure continuity of care, such as arranging continuation of care after discharge (97), telephone follow up and communication with primary providers at discharge (111), have been associated with a post-discharge reduction in A1C (111). Providing people with diabetes and their family or caregivers with written and oral instructions regarding their diabetes management at the time of hospital discharge will facilitate transition to community care. Comprehensive instructions may include recommendations for timing and frequency of home glucose monitoring; identification and management of hypoglycemia; a reconciled medication list, including insulin and other antihyperglycemic medications; and identification and contact information for health-care providers responsible for ongoing diabetes care and adjustment of glucose-lowering medications. Communication of the need for potential adjustments in insulin therapy that may accompany adjustments of other medications prescribed at the time of discharge, such as corticosteroids or octreotide, to people with diabetes and their primary care providers is important.

Safety

Hypoglycemia

Hypoglycemia remains a major barrier to achieving optimal glycemic control in hospitalized people with diabetes. Standardized treatment protocols that address mild, moderate and severe hypoglycemia may help mitigate this risk. Education of health-care workers about factors that increase the risk of hypoglycemia, such as sudden reduction in oral intake, discontinuation of parenteral or enteral nutrition, unexpected transfer from the nursing unit after rapid-acting insulin administration or a reduction in corticosteroid dose (78) are important steps to reduce the risk of hypoglycemia.

Insulin administration errors

Insulin is considered a high-alert medication and can be associated with risk of harm and severe adverse events. A systems approach that includes pre-printed, approved, unambiguous standard orders for insulin administration and/or a computerized order entry system may help reduce errors in insulin ordering (22).

RECOMMENDATIONS

1. An A1C should be measured if not done in the 3 months prior to admission on:
   a. All hospitalized people with a history of diabetes to identify individuals that would benefit from glycemic optimization [Grade D, Consensus]
   b. All hospitalized people with newly diagnosed hyperglycemia or those with diabetes risk factors to identify individuals at risk for ongoing dysglycemia [Grade C, Level 3 (16)]
   c. Repeat screening should be performed 6 to 8 weeks post-hospital discharge for individuals with an A1C 6.0–6.4% [Grade D, Consensus]
   d. In-hospital CBG monitoring should be initiated for individuals with an A1C ≥6.5% [Grade D, Consensus].
2. The frequency and timing of bedside CBG monitoring should be individualized for all in-hospital people with diabetes. Monitoring should typically be performed:
   a. Before meals and at bedtime in people who are eating [Grade D, Consensus]
   b. Every 4 to 6 hours in people who are NPO or receiving continuous enteral feeding [Grade D, Consensus]
   c. Every 1 to 2 hours for people on continuous intravenous insulin or those who are critically ill [Grade D, Consensus].
3. Provided that their medical conditions, dietary intake and glycemic control are stable, people with diabetes should be maintained on their pre-hospitalization noninsulin antihyperglycemic agents or insulin regimens [Grade D, Consensus].
4. For hospitalized people with diabetes treated with insulin, a proactive approach that includes basal, bolus and correction (supplemental) insulin, along with pattern management, should be used to reduce adverse events and improve glycemic control, instead of only correcting high BG with short- or rapid-acting insulin [Grade A, Level 1A (61,66,102)].
5. For the majority of noncritically ill hospitalized people with diabetes, preprandial BG targets should be 5.0 to 8.0 mmol/L in conjunction with random BG values <10.0 mmol/L, as long as these targets can be safely achieved [Grade D, Consensus].
6. For most medical/surgical critically ill hospitalized people with diabetes with hyperglycemia, a continuous intravenous insulin infusion should be used to maintain BG <10.0 mmol/L [Grade B, Level 2 (34)] and >6.0 mmol/L [Grade D, Consensus].
7. For people with diabetes undergoing CABG, a continuous intravenous insulin infusion protocol targeting intraoperative glycemic levels between 5.5 and 11.1 mmol/L should be used, rather than subcutaneous insulin, to prevent postoperative infections [Grade A, Level 1A (54)].
8. In hospitalized people with diabetes requiring insulin therapy, protocols using basal insulin with/without bolus insulin should be used for post-operative glycemic management [Grade B, Level 2 (61)].
9. In hospitalized people with diabetes, hypoglycemia should be minimized. Protocols for hypoglycemia avoidance, recognition and management should be implemented with nurse-initiated treatment, including glucagon for severe hypoglycemia when intravenous access is not readily available [Grade D, Consensus]. Hospitalized people with diabetes at risk of hypoglycemia should have ready access to an appropriate source of glucose (oral or IV) at all times, particularly when NPO or during diagnostic procedures [Grade D, Consensus].
10. Programs consisting of the following elements should be implemented for optimal inpatient diabetes care:
    a. Interprofessional team-based approach [Grade B, Level 2 (107,108,112)]
    b. Health-care professional development regarding in-hospital diabetes management [Grade D, Level 4 (95)]
    c. Algorithms, order sets and decision support [Grade C, Level 3 (26,99,105)].
    d. Comprehensive quality assurance initiatives, including institution-wide BG monitoring systems, inpatient education, and transition/continuity of care and discharge planning [Grade D, Consensus].

Abbreviations:
BG, blood glucose; *CBG*, capillary blood glucose; *CABG*, coronary artery bypass grafting; *CSII*, continuous subcutaneous insulin infusion; *ICU*, intensive care unit; *NPH*, neutral protamine Hagedorn; *POC*, point of care; *TDD*, total daily dose.

Other Relevant Guidelines

Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Hyperglycemic Emergencies in Adults, p. S109
Management of Acute Coronary Syndromes, p. S190
Treatment of Diabetes in People With Heart Failure, p. S196

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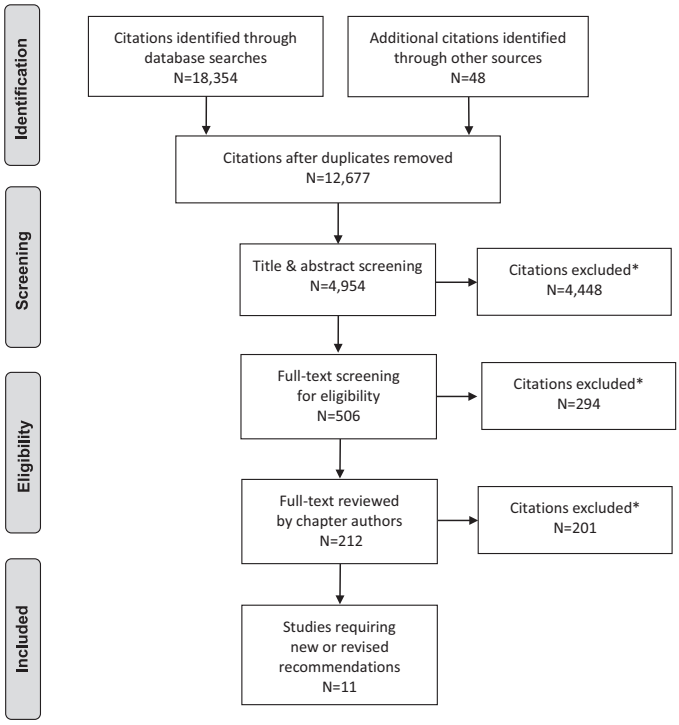
Literature Review Flow Diagram for Chapter 16: In-Hospital Management of Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (116).

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2018 Clinical Practice Guidelines

Weight Management in Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Sustained weight loss of ≥5% of initial body weight can improve glycemic control and cardiovascular risk factors.
- In people with diabetes and obesity, weight loss and A1C lowering can be achieved with healthy behaviour interventions as the cornerstone of treatment. Weight management medications can improve glycemic and metabolic control in people with diabetes and obesity.
- Bariatric surgery may be considered appropriate for people with diabetes and obesity.
- When selecting the most appropriate antihyperglycemic agent(s) for a person with diabetes, the effect on body weight should be considered.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- When you have diabetes, having overweight or obesity increases your risk for complications.
- Healthy behaviour modifications, including regular physical activity and eating well can help with your blood glucose control and reduce your risk for other health problems associated with diabetes.
- Your diabetes health-care team can help you with weight management. For some people with diabetes, weight management medications and bariatric surgery may be helpful.

Introduction

Obesity is a chronic health problem that is often progressive and difficult to treat. An estimated 80% to 90% of people with type 2 diabetes have overweight or obesity (1). Obesity is also becoming more prevalent in people with type 1 diabetes; one study reported a sevenfold increase in the last 20 years (2). In addition, intensive insulin therapy and some antihyperglycemic medications are associated with weight gain which, in turn, leads to obesity-related comorbid conditions (3,4). The relationship between increasing body fat accumulation and adverse health outcomes exists throughout the range of overweight and obesity in men and women of all age groups (5). Weight loss has been shown to improve glycemic control by increasing insulin sensitivity and glucose uptake and diminishing hepatic glucose output (6).

Assessment of Overweight and Obesity

Health Canada guidelines recommend that the initial assessment of people with diabetes should include the following measurements: height, weight, calculation of body mass index (BMI) (kg/m^2) and waist circumference (WC) (7) (Table 1). Metabolic comorbidities are highly correlated with increasing BMI and WC (8,9). Excessive abdominal adiposity is a strong independent predictor of metabolic comorbidities (10,11). Cut-off values for healthy WC vary among expert guidelines (12,13). Table 2 lists National Cholesterol and Education Program Adult Treatment Panel III (NCEP-ATP III) WC values. The International Diabetes Federation (IDF) has proposed population specific WC cut-off values; however, these guidelines have not been fully validated against the development of clinical events (14) (Table 3).

In people with diabetes and overweight or obesity, the reasons for the previous or current positive energy balance can often be identified. People with diabetes often take medications that are associated with weight gain; these include antihyperglycemic, antihypertensive, pain relief and antidepressant agents (15). Assessing psychological aspects of eating behaviours, such as emotional eating, binge eating, attention deficit and hyperactivity disorder (ADHD), and depression, is also relevant in determining reasons for weight gain (16). Physical parameters that impede activity, such as osteoarthritis or dyspnea, can contribute to obesity (17). Comorbid conditions, such as osteoarthritis and obstructive sleep apnea (OSA), can also impact the ability to lose weight (18).

Treatment of Overweight and Obesity

The goals of therapy for people with diabetes and overweight or obesity are to achieve optimal glycemic and metabolic control and, ultimately, improve quality of life, morbidity and mortality. Attaining and maintaining a healthy body weight, and preventing weight regain, are key components of optimizing glycemic control in people with diabetes. Often people with obesity and diabetes have greater difficulty with achieving weight loss compared to people with obesity but without diabetes (19). Health-care providers should attempt to minimize use of weight-inducing agents without compromising glycemic control, or switch the person with diabetes to agents not associated with weight gain (15).

For many people with diabetes, prevention of further weight gain is a realistic and sustainable target. A modest weight loss of 5% to

Conflict of interest statements can be found on page S127.

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Table 1
Canadian guidelines for body weight classification in adults using BMI

Classification	BMI* category (kg/m²)	Risk of developing health problems
Underweight	<18.5	Increased
Healthy weight	18.5–24.9	Least
Overweight	25.0–29.9	Increased
Obesity	≥30.0	
Class I	30.0–34.9	High
Class II	35.0–39.9	Very high
Class III	≥40.0	Extremely high

BMI, body mass index. Adapted from reference 74.
* BMI values are age and gender independent, and may not be correct for all ethnic populations.

Table 2
Waist circumference (WC) and risk of developing health problems

WC cut-off points*†	Risk of developing health problems
Men ≥102 cm	Increased
Women ≥88 cm	Increased

WC, waist circumference. Adapted from reference 74.
* WC cut-offs may be lower in some populations (e.g. older individuals, Asian population [see Table 3]), especially in the presence of the metabolic syndrome (such as hypertriglyceridemia).
† Increased WC can also be a marker for increased risk, even in persons with healthy weight.

10% of initial body weight can improve insulin sensitivity, glycemic control and blood pressure. Greater amounts of weight loss may be needed to improve OSA and dyslipidemia (20–24). The 2006 Canadian Obesity Guidelines have suggested a weight loss of 2 to 4 kg/month (25). A negative energy balance of approximately 500 kcal/day is needed to achieve this weight loss. Metabolic and physiologic adaptations following weight loss can promote weight regain and make sustained weight loss challenging (26). Adjustment of the caloric deficit may be required as weight loss progresses. In addition, as individuals lose weight, adjustment in antihyperglycemic medications may be required to avoid hypoglycemia (27).

The National Institutes of Health (NIH)-sponsored multicentre Look AHEAD (Action for Health in Diabetes) trial, investigated the effects of lifestyle intervention on changes in weight, fitness and cardiovascular (CV) risk factors and events in people with type 2 diabetes (28). The 8-year data revealed a 4.7% decrease in weight in the intensive lifestyle arm (29). This provided evidence that lifestyle changes can have a positive impact on weight change, fitness level and a decrease in medications, along with a small decrease in glycated hemoglobin (A1C) and other health benefits (29).

Table 3
Ethnic-specific values for waist circumference (WC)

Country or ethnic group	Central obesity as defined by WC	
	Men	Women
Europid*	≥94 cm	≥80 cm
South Asian, Chinese, Japanese	≥90 cm	≥80 cm
South and Central American	Use South Asian cutoff points until more specific data are available	
Sub-Saharan African	Use Europid cutoff points until more specific data are available	
Eastern Mediterranean and Middle East (Arab)	Use Europid cutoff points until more specific data are available	

Adapted from reference 11.
* NCEP-ATP III guidelines (9,78) and Health Canada (79) define central obesity as WC values ≥102 cm in men and ≥88 cm in women.

Table 4
Checklist for weight management programs

1. The program assesses and treats comorbid conditions.
2. The program recommends healthy behaviour modifications, and pharmacotherapy or surgery for those who qualify.
3. The program provides individualized nutritional, physical activity and behavioural programs and counselling.
4. Reasonable weight loss goals are set at 1–2 kg/month.
5. Cost is not prohibitive.
6. There is no requirement to buy products, supplements, vitamins or injections.
7. The program does not make unsubstantiated claims.
8. The program provides access to a weight maintenance program.

Adapted from reference 38.

Healthy Behaviour Interventions

Healthy behaviour interventions are essential components of successful weight management. (30,31). Interventions that combine dietary modification, increased and regular physical activity and behaviour therapy are the most effective at improving health outcomes (32–35). Structured interprofessional programs and group programs have demonstrated better results (34) compared to solo health-care professional-based interventions (36).

Dietary plans for people with diabetes should be evidence based and nutritionally adequate to ensure optimal health. Specific dietary recommendations for weight loss can be found in the Nutrition Therapy chapter, p. S64. Moderate carbohydrate reduction has been beneficial in people with diabetes, demonstrating improvements in high density lipoprotein (HDL) and triglycerides, blood glucose stability, and reductions in diabetes medication requirements (37).

People with obesity and diabetes benefit from advice by qualified professionals on appropriate serving sizes, caloric and carbohydrate intake and how to select nutrient-rich meals, as demonstrated by the Look AHEAD Study (28). Programs and clinics dedicated to weight management may be beneficial, particularly those that adhere to the checklist in Table 4 (38).

Pharmacotherapy

The effect of antihyperglycemic medication on body weight varies by class of medication. Some antihyperglycemic medications are associated with weight gain (insulin, insulin secretagogues, thiazolidinediones), and the magnitude of weight gain can vary from 4 to 9 kg or more (15,39,40) (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88). Insulin is associated with the most weight gain (41). Metformin, acarbose and DPP-4 inhibitors are typically weight neutral (15). Glucagon-like peptide-1 (GLP-1) receptor agonists are associated with a weight loss of about 3 kg in people with diabetes (42). Sodium-glucose co-transporter 2 (SGLT2) inhibitors are associated with a typical weight loss of 2 to 3 kg (43). People with type 1 diabetes may have a tendency toward slightly higher body weight with use of neutral protamine Hagedorn (NPH) insulin compared to long-acting basal insulin analogues (44).

Orlistat and liraglutide are the only approved medications for chronic weight management in Canada (42,45) (Table 5). When used to treat people with overweight or obesity and type 2 diabetes, both have been demonstrated to improve glycemic control and to reduce the doses of antihyperglycemic agents that promote weight gain (45). For people with type 2 diabetes or prediabetes, pharmacotherapy is indicated for chronic weight management with a BMI ≥27.0 kg/m², in whom healthy behaviour interventions have been unsuccessful or insufficient for improvement in health. Clinical trials with weight loss agents have confirmed a smaller degree of weight loss in people with diabetes compared to people with obesity without diabetes (42,46,47).

Table 5
Medications approved for the treatment of obesity in type 2 diabetes

Class	Relative weight loss	Side effects	Therapeutic considerations	Cost
Gastrointestinal lipase inhibitor (orlistat) (45)	↓	Loose stools, GI upset, rare liver failure	Oral medication, decreases fat absorption, may require vitamin supplementation	$$$
GLP-1 receptor agonist (liraglutide 3.0 mg) (42)	↓↓	Nausea, GI upset, rare gallstones and pancreatitis	Subcutaneous injectable, increases satiety	$$$$

GLP-1, Glucagon-like peptide-1.

Orlistat leads to greater weight loss when coupled with healthy behaviour interventions (45). It has been shown to be effective at improving glycemic and metabolic control in people with obesity and type 2 diabetes (45,48–50). In people with obesity and IGT, orlistat also improves glucose tolerance and reduces the progression to type 2 diabetes (19,51,52). Potential adverse effects include loose stools and other gastrointestinal side effects that may affect long-term compliance (53). Rare cases of fulminant liver failure have also been reported (54).

Liraglutide is a GLP-1 receptor agonist, which acts to increase satiety and decrease hunger in the brain. While most of the blood glucose lowering benefits of liraglutide are seen at 1.8 mg per day, there is an additional dose dependent weight loss effect up to 3.0 mg per day (42). Liraglutide is indicated at 1.2 or 1.8 mg per day for the treatment of type 2 diabetes, and at 3.0 mg per day for weight management in people with (42) or without type 2 diabetes (46). In people with type 2 diabetes, liraglutide 3.0 mg is effective to facilitate weight loss in addition to improving glycemic control and metabolic parameters, in combination with a lifestyle modification program (42,55,56). In people with prediabetes, liraglutide 3.0 mg is effective to delay progression to type 2 diabetes (46) (see Reducing the Risk of Developing Diabetes chapter, p. S20). Gastrointestinal side effects, including nausea, are generally transient in nature. Gallbladder disease and acute pancreatitis are rare potential complications of treatment (46).

Pharmacotherapy directed at weight management has not been adequately studied in people with type 1 diabetes.

Bariatric Surgery

Bariatric surgery is a therapeutic option in the management of people with type 2 diabetes and obesity. “Bariatric surgery” is the preferred term over “metabolic surgery”, as the benefits encompass metabolic, mechanical and psychological improvements. These procedures can result in sustained weight loss and significant improvements in obesity-related comorbidities, including control or remission of type 2 diabetes. Surgery is a treatment option for people with BMI ≥40.0 kg/m^2 or with BMI 35.0 to 39.9 kg/m^2 in the presence of comorbidities, such as type 2 diabetes, who have demonstrated an inability to achieve weight loss maintenance following an adequate trial of healthy behaviour interventions and/or pharmacotherapy. Evaluation for candidacy and appropriateness for surgical procedures includes assessment by an interdisciplinary team with medical, surgical, psychiatric and nutritional expertise (57). The benefits and risks of bariatric surgery must be carefully considered for each individual, and candidates must be prepared to comply with lifelong medical surveillance.

Commonly performed bariatric surgeries include Roux-en-Y gastric bypass (RYGB) (Figure 2), sleeve gastrectomy (Figure 1), and biliopancreatic diversion with or without duodenal switch (BPD/BPD-DS) (Figure 3). These procedures lead to sustained weight loss and improvements in or remission of type 2 diabetes (58–61). The likelihood of improvement in control or remission of type 2 diabetes is higher with Roux-en-Y gastric bypass surgery, sleeve gastrectomy or BPD compared to gastric banding (62–65). The gastric band has largely been abandoned in North America due to less

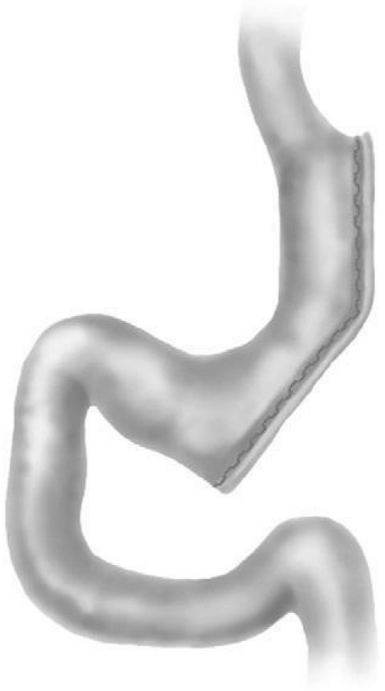

Figure 1. Gastric sleeve. A longitudinal (sleeve) resection of the stomach reduces the functional capacity of the stomach and eliminates the ghrelin-rich gastric fundus (80).

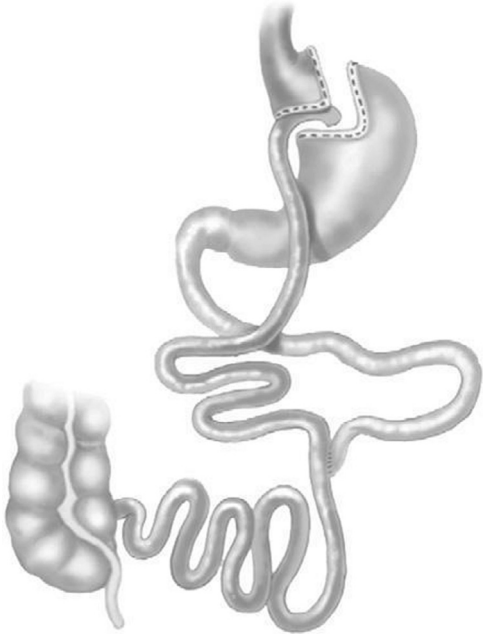

Figure 2. Roux-en-Y gastric bypass. A surgical stapler is used to create a small gastric pouch. Ingested food bypasses ~95% of the stomach, the entire duodenum and a portion of the jejunum (80).

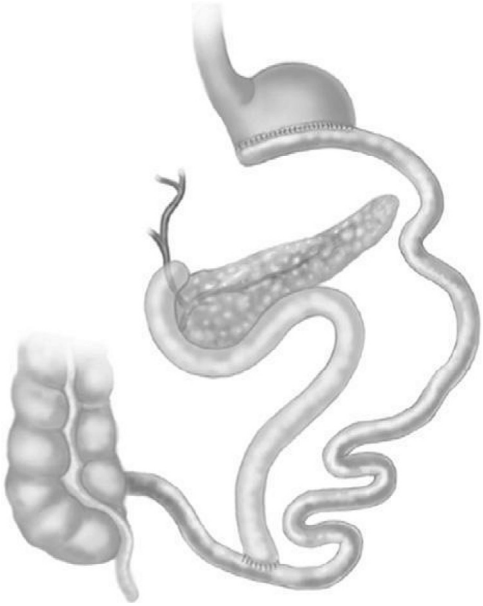

Figure 3. Biliopancreatic diversion with duodenal switch. The stomach and small intestine are surgically reduced so that nutrients are absorbed only in a 50-cm "common limb" (80).

sustained weight loss and metabolic benefits, and high surgical complication rates necessitating band removal (66).

Predictors of likelihood of remission of type 2 diabetes after bariatric surgery include higher preoperative serum C-peptide, younger age, shorter duration of diabetes and lack of need for insulin therapy preoperatively (67,68). People who experience remission of type 2 diabetes with bariatric surgery may experience recurrence of diabetes years later; thus, life-long monitoring and screening for recurrence is important (69). Evidence of the risks and outcomes of bariatric metabolic surgery in people with type 2 diabetes and BMI between 30 to 35 kg/m^2 is very limited and cannot be recommended at this time.

Bariatric surgery can prevent the development and progression of albuminuria (70). Studies have shown variable effects of bariatric surgery on diabetic retinopathy (71). One study has shown that bariatric surgery may reduce the risk of myocardial infarction in people with type 2 diabetes (72). Bariatric surgery has not been adequately studied in people with type 1 diabetes (73–76).

RECOMMENDATIONS

1. For people with overweight or obesity who have or are at risk for diabetes, an interprofessional weight management program is recommended to prevent weight gain and improve CV risk factors [Grade A, Level 1A (24,28)].

2. Weight management medication may be considered in people with diabetes and overweight or obesity to promote weight loss and improved glycemic control [Grade A, Level 1A (42) for liraglutide; Grade A, Level 1A (45) for orlistat].

3. In adults with type 2 diabetes and overweight or obesity, the effect of antihyperglycemic agents on body weight should be considered when selecting pharmacotherapy [Grade D, Consensus].

4. Bariatric surgery may be considered for selected adults with type 2 diabetes and obesity with BMI ≥35.0 when healthy behaviour interventions with or without weight management medication(s) are inadequate in achieving target glycemic control or healthy weight goals [Grade A, Level 1A (58,59,61)].

Abbreviations:
A1C, glycated hemoglobin; *BPD/BPD-DS*, biliopancreatic diversion with or without duodenal switch; *BMI*, body mass index; *CV*, cardiovascular; *CVD*, cardiovascular disease; *IGT*, impaired glucose tolerance; *LAGB*; laparoscopic adjustable gastric banding; *MI*, myocardial infarction; *RYGB*, Roux-en-Y gastric bypass; *WC*, waist circumference.

Other Relevant Guidelines

Reducing the Risk of Developing Diabetes, p. S20
Physical Activity and Diabetes, p. S54
Nutrition Therapy, p. S64
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88

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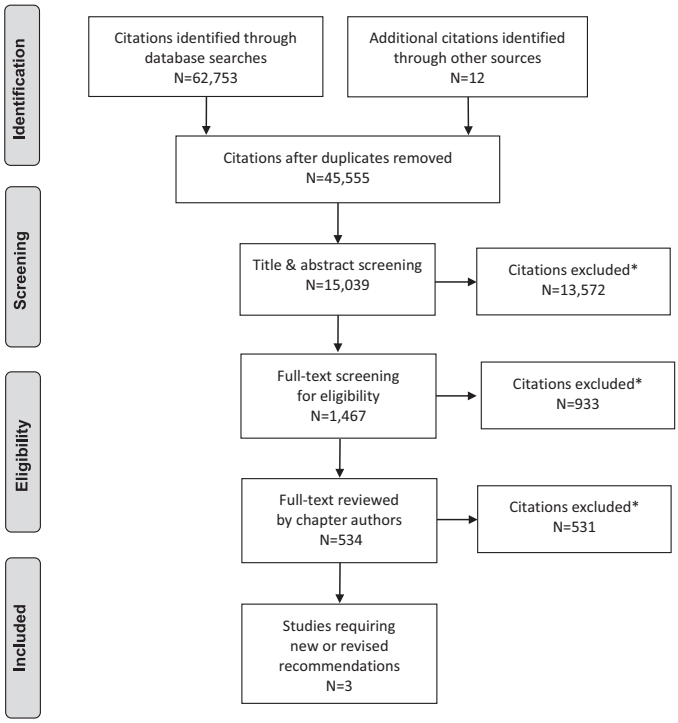
Literature Review Flow Diagram for Chapter 17: Weight Management in Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Diabetes and Mental Health

Diabetes Canada Clinical Practice Guidelines Expert Committee

David J. Robinson MD, FRCPC, FCPA, DFAPA, Michael Coons PhD, CPsych, CBSM, Heidi Haensel MD, FRCPC, Michael Vallis PhD, RPsych, Jean-François Yale MD, CSPQ, FRCPC

KEY MESSAGES

- The experience of living with diabetes is often associated with concerns specific to the illness and can cause conditions, such as diabetes distress, psychological insulin resistance and the persistent fear of hypoglycemic episodes.
- A wide range of psychiatric disorders, including major depressive disorder, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders, anxiety disorders, sleep disorders, eating disorders and stress-related disorders are more prevalent in people with diabetes compared to the general population.
- People living with diabetes and depressive disorders are at increased risk for earlier all-cause mortality compared to people living with diabetes without a history of depression.
- All individuals with diabetes should be regularly screened for the presence of diabetes distress, as well as symptoms of common psychiatric disorders.
- Compared to those with diabetes only, individuals with diabetes and mental health concerns have decreased participation in diabetes self-care, a decreased quality of life, increased functional impairment, increased risk of complications associated with diabetes, and increased health-care costs.
- Cognitive behaviour therapy, patient-centred approaches (e.g. motivational interviewing), stress management, coping skills training, family therapy and collaborative case management should be incorporated into primary care. Self-management skills, educational interventions that facilitate adaptation to diabetes, addressing co-occurring mental health issues, reducing diabetes-related distress, fear of hypoglycemia, and psychological insulin resistance are all helpful.
- Individuals taking psychiatric medications, particularly (but not limited to) atypical antipsychotics, benefit from regular screening of metabolic parameters to identify glucose dysregulation, dyslipidemia and weight gain throughout the course of the illness so that appropriate interventions can be instituted.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Living with diabetes can be burdensome and anxiety provoking, with the constant demands taking a psychological toll. As a result, many people experience distress, decreased mood and disabling levels of anxiety. Diabetes is often associated with a significant emotional burden, distress over the self-care regimen and stress in relationships (with family and friends, as well as health-care providers).
- It is important to recognize your emotions and talk to your friends, family and members of your diabetes health-care team about how you are feeling. Your team can help you to learn effective coping skills and direct you to support services that can make a difference for you.
- Mood and anxiety disorders are particularly common in people with diabetes. Eating, sleeping and stress-related disorders are also common. Speak to your health-care providers about any concerns you have if you think you may be developing any of these problems.
- Mental health disorders can affect your ability to cope with and care for your diabetes. In view of this, it is just as important to look after your mental health as it is your physical health.
- People diagnosed with serious mental illnesses, such as major depressive disorder, bipolar disorder and schizophrenia, have a higher risk of developing diabetes than the general population.

Introduction

Research has shown an increasingly clear relationship between diabetes and a variety of mental health issues. These include diagnosable psychiatric disorders, and other problems that are specific to the experience of living with diabetes. “Diabetes distress” refers to the negative emotions and burden of self-management related to living with diabetes. This term is used to describe the despondency and emotional turmoil specifically related to living with diabetes, in particular the need for continual monitoring and treatment, persistent concerns about complications, and the potential erosion of personal and professional relationships (1,2). “Psychological insulin resistance” is the reluctance or refusal to initiate insulin therapy, which may delay the start of a necessary treatment for a period of time (3). Fear of hypoglycemia is another common diabetes-specific concern. The presence of psychiatric and diabetes-specific psychosocial issues is associated with reduced participation in self-management activities and can lead to a decrease in quality of life. Psychiatric disorders among individuals with diabetes increases the risk of diabetes complications and early mortality (4).

Psychological Effects of Diabetes in Adults

Diabetes is a demanding chronic disease for both individuals and their families (5). It is associated with a number of challenges, including adjusting to a new diagnosis, diabetes distress impairing self-management, psychological insulin resistance, and fear of hypoglycemia. In addition, a range of psychiatric disorders can arise that contributes to greater complexity in both assessment and treatment. For instance, distinguishing between diabetes distress, major depressive disorder (MDD) and the presence of depressive symptoms

Conflict of interest statements can be found on page S137.

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Table 1
Comparison of main features and assessment methods: diabetes distress vs. major depressive disorder

	Diabetes Distress	Major Depressive Disorder
Assessment Instrument	Diabetes Distress Scale (17 items) (2)	Patient Health Questionnaire for Depression: PHQ-9 (9 items) (167,168)
Format	Self-report using ratings from 1 to 6 based on feelings and experiences over the past week	Self-report using ratings from 0 to 3 based on feelings and experiences over the past 2 weeks
Features	Emotional Burden Subscale (5 items) Physician-Related Distress Subscale (4 items) Regimen-Related Distress Subscale (5 items) Diabetes-Related Interpersonal Distress Subscale (3 items)	Vegetative symptoms, such as sleep, appetite and energy level changes Emotional symptoms, such as low mood and reduced enjoyment of usual activities Behavioural symptoms, such as agitation or slowing of movements Cognitive symptoms, such as poor memory or reduced concentration or feelings of guilt; thoughts of self-harm

CBT, cognitive behavioural therapy.

is important. Although these constructs have some shared symptomatology, diabetes distress has been most shown to have the strongest effect in causing adverse diabetes outcomes (6–9) (Table 1).

Diabetes distress is comprised of 4 interconnected domains, which include: 1) the emotional burden of living with diabetes; 2) the distress associated with the diabetes self-management regimen; 3) the stress associated with social relationships; and 4) the stress associated with the patient-provider relationship. Diabetes distress is associated with elevated glycated hemoglobin (A1C levels), higher diastolic blood pressure (BP) and increased low-density lipoprotein cholesterol (LDL-C) levels (10–12). Furthermore, individuals with higher levels of diabetes distress were found to have a 1.8-fold higher mortality rate, a 1.7-fold increased risk of cardiovascular (CV) disease (13), and have lower quality of life (14). Risk factors for developing diabetes distress include being younger, being female, having lower education, living alone, having a higher body mass index (BMI), lower perceived self-efficacy, lower perceived provider support, poorer quality diet, greater perceived impact of glycemic excursions and greater number of diabetes complications (15,16).

Psychological insulin resistance refers to a strong negative response to the recommendation from health-care providers that a person may benefit from adding insulin to his or her diabetes regimen. This can be a common reaction, particularly for individuals with type 2 diabetes who may have previously been successfully managed with noninsulin antihyperglycemic agents. Individuals may hold maladaptive beliefs that requiring insulin is a sign of personal failure in their self-management, or that their illness has become much more serious. Further, many people report fear and anxiety about having to self-administer injections, or have a low level of confidence in their ability to manage their blood glucose with insulin (17,18).

Fear of hypoglycemia is a common occurrence. Hypoglycemic experiences, especially serious or nocturnal episodes, can be traumatic for both individuals and their family members. A common strategy to minimize fears of hypoglycemia is compensatory hyperglycemia, where individuals either preventatively maintain a higher blood glucose (BG) level, or treat hypoglycemia in response to perceived somatic symptoms without objective confirmation by capillary blood glucose concentrations (19–22). Over time, this maladaptive process, if left unmanaged, can negatively impact diabetes control, increase the risk of CV complications, and reduce quality of life.

Challenges accompanying the diagnosis of diabetes include adjustment to the illness, participation in the treatment regimen and psychosocial difficulties at both a personal and an interpersonal level (23,24). Stress, deficient social supports and negative attitudes toward diabetes can impact on self-care and glycemic control (25–29). Diabetes management strategies ideally incorporate a means of addressing the psychosocial factors that impact on individuals and their families. Both symptom measures (e.g. self-report measures of various symptoms) and methods to arrive at psychiatric diagnoses (e.g. structured interviews leading to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-5 diagnoses] (30) have been assessed. Given that the person with diabetes is directly responsible for 95% of diabetes management (31), identifying significant psychological reactions in diabetes is important since depressive symptoms are a risk factor for poor diabetes self-management (32–34) and outcomes, including early mortality (35,36).

Psychiatric Conditions in Adults

Individuals with serious mental illnesses, particularly those with depressive symptoms or syndromes, and people with diabetes share reciprocal susceptibility and a high degree of comorbidity (Figure 1). The mechanisms behind these relationships are multifactorial, complicated and presently only partially understood. Some evidence shows that treatment for mental health disorders may actually increase the risk of diabetes, particularly when second- and third-generation (atypical) antipsychotic agents are prescribed (37). Biochemical changes due to psychiatric disorders themselves also may play a role (38). Symptoms of mental health disorders and their impact on lifestyle are also likely to be contributing factors (39).

Major Depressive Disorder

The prevalence of clinically relevant depressive symptoms among people with diabetes is approximately 30% (40–42). The prevalence of MDD is approximately 10% (43,44), which is double the overall prevalence in people without a chronic medical illness. The risk of developing MDD increases the longer a person has diabetes (45). Clinically identified diabetes was associated with a doubling of the prescriptions for antidepressants, but undiagnosed diabetes was not, consistent with the hypothesis that the relationship between diabetes and depression may be attributable to factors related to diabetes management (46). Individuals with depression have an approximately 40% to 60% increased risk of developing type 2 diabetes (46–48). The prognosis for comorbid depression and diabetes is worse than when each illness occurs separately (3). Depression in people with diabetes amplifies symptom burden by a factor of about 4 (49). Episodes of depression in individuals with diabetes are likely to last longer and have a higher chance of recurrence compared to those without diabetes (50). Episodes of severe hypoglycemia have been correlated with the severity of depressive symptoms (51,52). Major depressive disorder has been found to be underdiagnosed in people with diabetes (53).

Studies examining differential rates for the prevalence of depression in type 1 vs. type 2 diabetes have yielded inconsistent results (40,54). One study found that the requirement for insulin was the factor associated with the highest rate of depression,

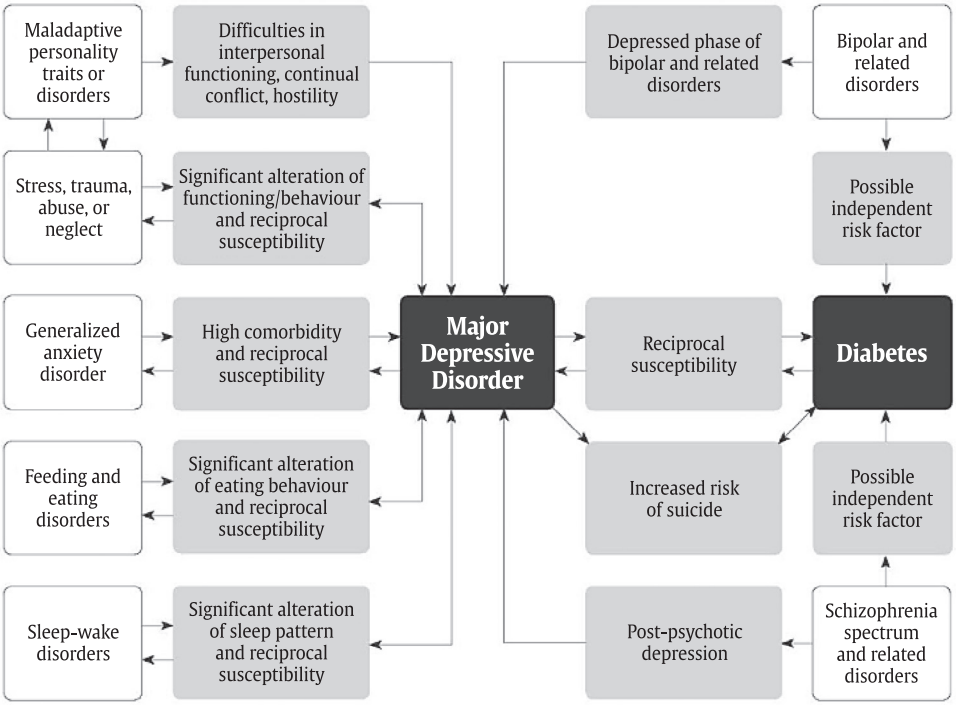

Figure 1. The interplay between diabetes, major depressive disorder and other psychiatric conditions.

regardless of the type of diabetes involved (55). Treatment with metformin may enhance recovery from MDD (56).

Risk factors for developing depression in individuals with diabetes are as follows (57–61):

- Female sex
- Adolescents/young adults and older adults
- Poverty
- Few social supports
- Stressful life events
- Poor glycemic control, particularly recurrent hypoglycemia
- Higher illness burden
- Longer duration of diabetes
- Presence of long-term complications.

Intensive lifestyle intervention for people with type 2 diabetes with overweight or obesity reduced the risk of depressive symptoms by 15% (62).

Risk factors (with possible mechanisms) for developing diabetes in people with depression are as follows:

- Physical inactivity (63) and overweight/obesity, which leads to insulin resistance
- Psychological stress leading to chronic hypothalamic-pituitary-adrenal dysregulation and hyperactivity stimulating cortisol release, also leading to insulin resistance (64–69)
- Hippocampal atrophy and decreased neurogenesis (70).

Some of the mechanisms underlying this association have been found to be: autonomic and neurohormonal dysregulation, hippocampal structural changes, inflammatory processes and oxidative stress (70).

Comorbid depression worsens clinical outcomes in diabetes, possibly because the accompanying lethargy lowers motivation for self-care, resulting in lowered physical and psychological fitness, higher use of health-care services and reduced participation in medication regimens (71,72). Depression also appears to worsen CV mortality (73–75). Treating depressive symptoms more reliably improves mood than it does glycemic control (76–79).

Bipolar Disorder

One study demonstrated that over half of people with bipolar disorder were found to have impaired glucose metabolism, which was found to worsen key aspects of the course of the mood disorder (80). In this same study, impaired glucose tolerance (IGT) was deemed to be an etiologic factor in the development of bipolar disorder (80). People with bipolar disorder have been found to have prevalence rates estimated to be double that of the general population for metabolic syndrome and triple for diabetes (81–84). Insulin resistance is associated with a less favourable course of bipolar illness, more cycling between mood states, and a poorer response to lithium (85).

Schizophrenia Spectrum Disorders

Schizophrenia and other psychotic disorders may contribute an independent risk factor for diabetes. People diagnosed with psychotic disorders were reported to have had insulin resistance/glucose intolerance prior to the advent of antipsychotic medication, although this matter is still open to debate (86–88). The Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) study found that of the individuals with schizophrenia who participated in the study, 11% had diabetes at baseline (type 1 and 2 combined) (37). The prevalence of metabolic syndrome was approximately twice that of the general population (89). Diabetes and schizophrenia together lead to more CV complications and all-cause mortality compared to people with diabetes alone (90). Whether the increased prevalence of diabetes is due to the effect of the illness (such as advanced glycation end products), antipsychotic medications or other factors, individuals with psychotic disorders represent a particularly vulnerable population (91).

Personality Traits/Disorders

Personality traits or disorders that put people in constant conflict with others or engender hostility have been found to increase the risk of developing type 2 diabetes (92). People with chronic, significantly negative mood states and social inhibition were less likely to follow a healthy diet or to consult health-care professionals in case problems developed with their diabetes management. They report more barriers surrounding medication use, diabetes-specific social anxiety, loneliness and symptoms of depression and anxiety (93).

Stress, Trauma, Abuse and Neglect

A history of significant adversity/trauma, particularly early in life, increases the risk of obesity, diabetes and CV disease (94). Higher BMI, leptin, BP, fibrinogen and decreased insulin sensitivity have been found (95). Post-traumatic stress disorder (PTSD) was found to cause a 40% increased risk of developing type 2 diabetes; those with sub-syndromal traumatic stress symptoms had a 20% increased risk (96).

Anxiety

Anxiety is commonly comorbid with depressive symptoms (97). One study estimated that 14% of individuals with diabetes suffered from generalized anxiety disorder, with double this figure experiencing a subclinical anxiety disorder and triple this figure having at least some anxiety symptoms (98). Anxiety disorders were found in one-third of people with serious mental illnesses and type 2 diabetes, and were associated with increased depressive symptoms and decreased level of function (99). Long-term anxiety has been associated with an increased risk of developing type 2 diabetes (100).

Feeding and Eating Disorders

Anorexia nervosa, bulimia nervosa and binge-eating disorder have been found to be more common in individuals with diabetes (both type 1 and type 2) than in the general population (101). Eating disorders are common and persistent, particularly in females with type 1 diabetes (102,103). Elevated BMI is a risk factor for developing type 2 diabetes and MDD (104). Depressive symptoms are highly comorbid with eating disorders, affecting up to 50% of individuals (105). Night eating syndrome is characterized by the consumption of >25% of daily caloric intake after the evening meal and waking at night to eat, on average, at least 3 times per week. Night eating syndrome has been noted to occur in individuals with type 2 diabetes and depressive symptoms. Night eating syndrome can result in weight gain, poor glycemic control and an increased number of diabetes complications (106).

Sleep-Wake Disorders

People with sleep apnea develop diabetes at higher rates than those without the condition (107).

Substance Use Disorders

The exact prevalence of substance use disorders among individuals with diabetes is not well established, and the presence of substance use disorders may contribute to unique challenges in this population. Recreational substance abuse was associated with increased rates of hospitalization and readmissions for DKA (108). Furthermore, substance abuse and psychosis among individuals with type 1 and type 2 diabetes increases the risk of all-cause mortality (109).

Children and Adolescents with Diabetes

For children, and particularly adolescents, there is a need to identify mental health disorders associated with diabetes and to intervene early to minimize the impact over the course of development. Children and adolescents with type 1 diabetes have significant risks for mental health problems, including depression, anxiety, eating disorders and disruptive behaviour disorders (110–112). The risks increase significantly during adolescence (113,114). Studies have shown that mental health disorders predict poor diabetes management and control (115–118) and worsen medical outcomes (32,119–121). Conversely, as glycemic control worsens, the probability of mental health problems increases (122). Adolescents with type 1 diabetes have been shown to have generally comparable rates for diabetes distress compared to adults with type 1 diabetes (1).

The presence of psychological symptoms and diabetes problems in children and adolescents with type 1 diabetes are often strongly affected by caregiver/family distress. It has been demonstrated that while parental psychological issues are often related to poor psychological adjustment and diabetes control (123–126), they also distort perceptions of the child's diabetes control (127). Maternal anxiety and depression are associated with poor diabetes control in younger adolescents with type 1 diabetes and with reduced positive effects and motivation in older teens (128).

Feeding and Eating Disorders in Pediatric Diabetes

Ten per cent of adolescent females with type 1 diabetes met the *Diagnostic and Statistical Manual of Mental Disorders* (5th Edition) criteria for eating disorders (30), compared to 4% of their age-matched peers without diabetes (128). Eating disorders are also associated with poorer metabolic control, earlier onset and more rapid progression of microvascular complications (103). In adolescent and young adult females with type 1 diabetes who are unable to achieve and maintain glycemic targets, particularly if insulin omission is suspected, an eating disorder may be a potential cause. Individuals with eating disorders may require different management strategies to optimize glycemic control and prevent microvascular complications (129). Type 1 diabetes in young adolescent women appears to be a risk factor for development of an eating disorder, both in terms of an increased prevalence of established eating disorder features as well as through deliberate insulin omission or underdosing (called diabulimia) (130,131).

Other Considerations in Children and Adolescents

The prevalence of anxiety disorders in children and adolescents with type 1 diabetes in 1 study was found to be 15.5%, and mood disorders was 3.5%, with one-third having a lifetime prevalence of at least one psychiatric condition (132). The presence of psychiatric disorders was related to elevated A1C levels and a lowered health-related quality of life score in the general pediatric quality of life inventory. In the diabetes mellitus-specific pediatric quality of life inventory, children with psychiatric disorders revealed more symptoms of diabetes, treatment barriers and lower adherence than children without psychiatric disorders (132). Adolescents with type 1 diabetes ranked school as their number 1

stressor, their social lives as number 2 and having diabetes as number 3 (133).

Prevention and Intervention

Children and adolescents with diabetes, along with their families, should be screened throughout their development for mental health disorders (134). Given the prevalence of mental health issues, screening in this area is just as important as screening for microvascular complications in children and adolescents with diabetes (135).

Psychological interventions with children and adolescents, as well as families, have been shown to improve mental health (136), including overall well-being and perceived quality of life (137), along with reducing depressive symptoms (138). In addition, there is evidence to show that psychosocial interventions can positively affect glycemic control (139,140). Most importantly, some studies have demonstrated that psychological interventions can increase both diabetes treatment adherence and glycemic control, as well as psychosocial functioning (141,142).

Type 2 Diabetes in Children and Adolescents

Atypical antipsychotic medications are associated with significant weight gain, insulin resistance, IFG and type 2 diabetes in children (143). Psychiatric disorders and the use of psychiatric medications are more common in children with obesity at diagnosis of type 2 diabetes compared to the general pediatric population (144). Children and adolescents prescribed an atypical antipsychotic have double the risk of developing diabetes (145). The risk of developing diabetes may be higher in adolescents taking concomitant antipsychotic and antidepressant medications (146).

Considerations in Pregnancy

One study found that gestational diabetes was strongly associated with increased risk for postpartum depression (PPD), regardless of prior depression history, whereas pregestational diabetes increased risk only for those with a prior history of depression. It was also found that for those with a history of depression, diabetes adds a 1.5-fold increased risk for PPD (147). Optimized glycemic control in pregnancy has been shown to have numerous benefits for pregnancy outcomes and may also be protective against PPD (148,149). In another study, the presence of depressive symptoms in early pregnancy was associated with preterm delivery in women with pregestational diabetes (150). Thus, there may be a role for improved screening and treatment of depression in optimizing pregnancy outcomes in women with diabetes (151).

Considerations for Older People with Diabetes

Type 2 diabetes does not appear to be more common in geriatric psychiatric patients than similarly aged controls. MDD and the use of antidepressants, cholinesterase inhibitors and valproate may increase fasting glucose levels (152). The risk of developing a dementing illness in people is increased with those who have MDD (hazard ratio [HR 1.83], type 2 diabetes [HR 1.20] or both [HR 2.17]) (153). The presence of depressive symptoms in elderly people with type 2 diabetes is associated with increased mortality risk (154).

Suicide

A review article found that people with both type 1 and type 2 diabetes had increased rates of suicidal ideation, suicide attempts and completed suicide compared to the general population (155). Another study found that people with newly diagnosed type 2 diabetes had a rate of past suicide attempts of almost 10%, which is twice the rate estimated in the general population. The rate of past suicide attempts in currently depressed patients with diabetes was reported at over 20% (156).

Psychiatric Disorders and Adverse Outcomes

Two independent systematic reviews with meta-analyses showed that MDD significantly increases the risk of all-cause mortality among individuals with diabetes compared to those with diabetes without it (157,158). Older adults with diabetes and depression may be at particular risk (109). Individuals with bipolar disorder, schizophrenia or other psychotic disorders, and who have comorbid diabetes, are at increased risk of rehospitalization following medical-surgical admissions (159).

Screening and Assessment of Mental Health Symptoms

Because of the prevalence of diabetes distress and psychiatric comorbidity and the negative impact that these factors have on glycemic control, early morbidity and quality of life, it is recommended that individuals with diabetes should be regularly screened with validated questionnaires or clinical interviews. The available data does not currently support the superiority of any particular depression screening tool (160). Currently available screening instruments have a sensitivity of between 80% and 90% and a specificity of 70% to 85% (160). Scales that are in the public domain are available at www.outcometracker.org/scales_library.php. Patient Health Questionnaire (PHQ) Screeners are available at www.phqscreeners.com. PHQ-9 (for MDD) scores of ≥10 and Generalized Anxiety Disorders (GAD)-7 scores ≥10 have been associated with increased diabetes complications (161,162).

Screening instruments fall into 3 categories:

- Diabetes-specific measures, such as the Problem Areas in Diabetes (PAID) Scale or the Diabetes Distress Scale (DDS) (163,164)
- Quality of life measures, such as the WHO-5 screening instrument (165)
- Depressive/anxiety symptoms, such as the Hospital Anxiety and Depression Scale (HADS) (166), the Patient Health Questionnaire (PHQ-9) (167,168), the Centre for Epidemiological Studies-Depression Scale (CES-D) (169) or the Beck Depression Inventory (BDI) (170).

Table 1 outlines the principal features and assessment methods to differentiate diabetes distress from MDD.

Psychosocial (Non-Pharmacological) Treatments

Efforts to promote well-being to mitigate distress should be incorporated into diabetes management for all individuals (171). Motivational interventions (172,173), coping skills, self-efficacy enhancement, stress management (174,175) and family interventions (176–179) all have been shown to be helpful. Case management by a nurse working with the patient's primary care provider and providing guideline-based, patient-centred care resulted in improved A1C, lipid levels, BP and depression scores (172,180–182). Individuals with diabetes distress and/or psychiatric disorders benefit from professional interventions, either some form of psychotherapy or prescription medication. Evidence from systematic reviews of randomized controlled trials supports cognitive behaviour

Table 2
Features of CBT that can be applied to diabetes treatment

Cognitive Component	Behavioural Component
Record keeping to identify distressing automatic thoughts	Strategies to help get the person moving (behavioural activation)
Understanding the link between thoughts and feelings	Scheduling pleasant and meaningful events
	Learning assertive and effective communication skills
Learning the common "thinking errors" that mediate distress (e.g. all-or-nothing thinking, personalization, magnification, minimization, etc.)	Focusing on feelings of mastery and accomplishment
Analyzing negative thoughts and promoting more functional ones	Learning problem-solving strategies
Identifying basic assumptions about oneself (e.g. "unless I am very successful, my life is not worth living) and being encouraged to adopt healthier ones (e.g. "when I am doing my best, I should be proud of myself")	Exposure to new experiences
	Shaping behaviours by breaking them down into smaller steps to develop skills

CBT, cognitive behavioural therapy.

therapies (CBT) and antidepressant medication, both solely or in combination (138,183,184). No evidence presently shows that the combination of CBT and medication is superior to these treatments given individually. A pilot study of 50 people with type 2 diabetes who initially had a moderate level of depression at baseline showed an improvement in the severity of their depression (moving to the mild range) with a 12-week intervention of 10 CBT sessions combined with exercise in the form of 150 minutes of aerobic activity weekly. This effect was sustained at 3 months (138).

Table 2 illustrates some of the major features of CBT as applied to diabetes care. Gains from treatment with psychotherapy are more likely to benefit psychological symptoms and glycemic control in adults than will psychiatric medications (which usually reduce psychological symptoms only) (185). Meta-analyses of psychological interventions found that they improved glycemic control (A1C) in children and adolescents with type 1 diabetes (186), and adults with type 2 diabetes (187). Furthermore, evidence suggests interventions are best implemented in a collaborative fashion and when combined with self-management interventions (185). Recent evidence also supports the effectiveness of mindfulness-based CBT (188,189).

Among adults with type 2 diabetes and subclinical depression, CBT resulted in reductions in diabetes distress and depressive symptoms compared to controls (190). Lower diabetes regimen distress (produced by an intervention combining education, problem solving and support for accountability) led to improvements in medication adherence, physical activity and decreased A1C over 1 year (191,192).

Recent research suggests that CBT can be used to address psychological insulin resistance by specifically addressing the beliefs that underlie it (3,193–195) (Figure 2). Fear of hypoglycemia is amenable to treatment, such as with the behavioural desensitization process illustrated in Figure 3 (21,22,195,196).

Since diabetes outcomes are heavily dependent on the sustained participation of the individual with the illness, motivational and behavioural change strategies can be effective. Diabetes care providers can enhance successful behaviour changes through motivational strategies, such as having individuals weigh the advantages and disadvantages of change, as well as encouraging their sense of self-efficacy (197–199). Optimism and compassion have been shown to be helpful (200,201).

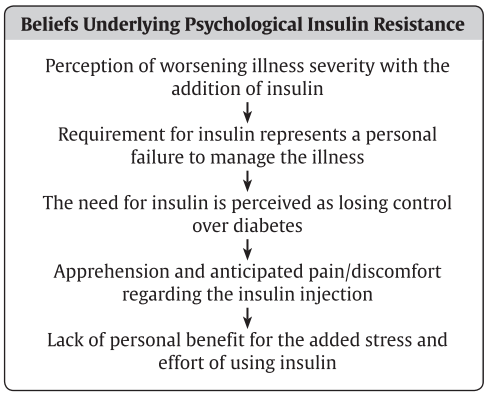

Figure 2. Features of psychological insulin resistance.

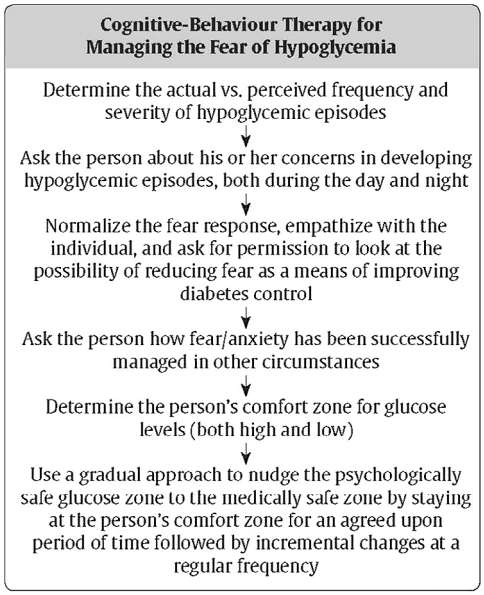

Figure 3. Suggested cognitive behaviour therapy for fear of hypoglycemia.

Pharmacological Treatments

Psychiatric medications have the capacity to affect metabolic parameters and cause changes in weight, glycemic control, lipid profile and can have immunomodulating effects (202–205). A systematic review estimated and compared the effects of antipsychotics, both novel and conventional, and noted variable effects on weight gain (206). The weight gain potential of clozapine and olanzapine has been established (207,208). Children and adolescents using antipsychotics had a 2- to 3-fold increased risk of type 2 diabetes (209,210), which was apparent within the first year of follow up. Metformin has been shown to have a modest ability to reduce weight gain due to antipsychotic medication (211).

A comprehensive review and meta-analysis looked at the effect of antidepressants on body weight (212). Serotonin-norepinephrine reuptake inhibitors (SNRIs) are generally more active on the serotonergic component, with levomilnacipran having the strongest preference among the group for blocking norepinephrine reuptake. Desipramine is the tricyclic antidepressant (TCA) with the strongest action in blocking norepinephrine reuptake (213), and has the potential to affect glucose homeostasis.

The CATIE study investigated 4 aspects of the effectiveness of antipsychotic medications: efficacy, tolerability, emergence of

medical problems and patient choice (67). The results did indicate that some antipsychotic medications were more likely to cause weight gain, worsen glycemic control and induce unfavourable changes in lipid profile. However, when these effects were considered in the context of efficacy, tolerability and patient choice, no conclusive statements could be made about which medications to clearly use or avoid. Consequently, all 4 aspects are important and reinforce the need for regular and comprehensive metabolic monitoring. Non-pharmacological interventions can be effective in reducing antipsychotic-associated weight gain and glucose changes (214).

Should medical problems arise while a person is taking psychiatric medications, clinical judgement will dictate on a case-by-case basis whether healthy behaviour interventions, such as diet or exercise, adding a medication to address the emergent issue (e.g. side effect or medical complication) or changing the psychiatric prescription is the most reasonable step (215,216). Resources are available to help clinicians quickly review the major side effect profiles of psychiatric medications (217,218).

Monitoring Metabolic Risks

Metabolic syndrome is found at higher rates in individuals with psychiatric illnesses than in the general population (84,219). Patients with diabetes and comorbid psychiatric illnesses are at an elevated risk for developing metabolic syndrome, possibly due to a combination of the following factors (220):

- Patient factors (e.g. health behaviour choices, diet, tobacco consumption, substance use, exercise, obesity, low degree of implementation of education programs)
- Illness factors (e.g. pro-inflammatory states from MDD or depressive symptoms, possible disease-related risks for developing diabetes) (221,222)
- Medication factors (e.g. psychiatric medications have variable effects on glycemic control, weight and lipids)
- Environmental factors (e.g. access to health care, availability of screening and monitoring programs, social supports, education programs).

Table 3
Psychiatric medications and risk of weight gain

	Unlikely		Likely	Very Likely		Highly Likely
Anticholinergics	Benztropine	Trihexyphenidyl	Procyclidine			Diphenhydramine
Antidepressants	Bupropion Citalopram Desvenlafaxine Duloxetine Escitalopram Fluoxetine	Levomilnacipran Moclobemide Sertraline Trazodone Venlafaxine Vortioxetine	Paroxetine Tranylcypromine	Amitriptyline Clomipramine Desipramine Doxepin Fluvoxamine Imipramine	Maprotiline Mirtazapine Nortriptyline Phenelzine Trimipramine	
Antipsychotics	Aripiprazole Brexpiprazole Loxapine	Thiothixene Trifluoperazine Ziprasidone	Asenapine Fluphenazine Haloperidol Methotrimeprazine Pericyazine Perphenazine Pimozide	Amoxapine Chlorpromazine Flupenthixol Lurasidone Paliperidone	Pipotiazine Quetiapine Risperidone Thioridazine Zuclopenthixol	Clozapine Olanzapine
Anxiolytics	Clonazepam Clorazepate Diazepam Flurazepam Lorazepam	Nitrazepam Oxazepam Temazepam Triazolam				
Cholinesterase inhibitors	Donepezil Galantamine	Rivastigmine				
Mood stabilizers	Lamotrigine	Topiramate	Carbamazepine Gabapentin Oxcarbazepine	Lithium	Valproate	
Sedatives / hypnotics	Zolpidem	Zopiclone				
Stimulants	Atomoxetine Dextroamphetamine Lisdexamfetamine	Methylphenidate Modafinil				
Substance use disorder treatments	Buprenorphine Clonidine	Naltrexone Varenicline	Methadone			

Amalgamated from references 217 and 218.

Table 4
Psychiatric medication metabolic monitoring protocol

Parameter	Baseline	1 month	2 months	3 months	Every 3 to 6 months	Annually
Weight (BMI)	x	x	x	x	x	
Waist circumference	x			x		x
Blood pressure	x			x		x
A1C preferred ± Fasting Plasma Glucose	x			x	x	
Fasting lipid profile	x			x	x	
Personal history, particularly alcohol, tobacco and recreational substance use	x			x		x
Family history	x					x

A1C, glycated hemoglobin; *BMI*, body mass index.

Many psychiatric medications (primarily second- and third-generation or atypical antipsychotics), have the potential to affect weight, lipids and glycemic control even in patients without diabetes (37,223). A weight gain of between 2 to 3 kg was found within a 1-year time frame with the antidepressants amitriptyline, mirtazapine and paroxetine (212). A study of people with type 2 diabetes and schizophrenia who were treated with antipsychotic medications also showed worsening glycemic control, requiring the addition of insulin therapy over a 2-year period with a HR of 2.0 (224). The reported weight gain over a 1-year period ranges from <1 kg to >4 kg for various antipsychotic medications. The main impact on lipid profile is an increase in triglyceride and total cholesterol levels, especially with clozapine, olanzapine and quetiapine (37,225). Table 3 lists the likelihood for weight gain with use of psychiatric medications.

Regular, comprehensive monitoring of metabolic parameters is recommended for all persons who receive antipsychotic medications, whether or not they have diabetes. A1C was shown to be a more stable parameter in identifying psychiatric patients with diabetes (226). Table 4 outlines a Psychiatric Medication Metabolic Monitoring Protocol.

RECOMMENDATIONS

1. Individuals with diabetes should be regularly screened for diabetes-related psychological distress (e.g. diabetes distress, psychological insulin resistance, fear of hypoglycemia) and psychiatric disorders (e.g. depression, anxiety disorders) by validated self-report questionnaire or clinical interview [Grade D, Consensus]. Plans for self harm should be asked about regularly as well [Grade C, Level 3 (155)].

2. The following groups of people with diabetes should be referred to specialized mental health-care professionals [Grade D, Consensus for all of the following]:
   a. Significant distress related to diabetes management
   b. Persistent fear of hypoglycemia
   c. Psychological insulin resistance
   d. Psychiatric disorders (i.e. depression, anxiety, eating disorders).

3. Collaborative care by interprofessional teams should be provided for individuals with diabetes and depression to improve:
   a. Depressive symptoms [Grade A, Level 1 (181,182)]
   b. Adherence to antidepressant and noninsulin antihyperglycemic medications [Grade A, Level 1 (181)]
   c. Glycemic control [Grade A, Level 1 (182)].

4. Psychosocial interventions should be integrated into diabetes care plans, including:
   a. Motivational interventions [Grade D, Consensus]
   b. Stress management strategies [Grade C, Level 3 (175)]
   c. Coping skills training [Grade A, Level 1A (227) for type 2 diabetes; Grade B, Level 2 (228) for type 1 diabetes]
   d. Family therapy [Grade A, Level 1B (176,178,229)]
   e. Case management [Grade B, Level 2 (192)].

5. Antidepressant medication should be used to treat acute depression in people with diabetes [Grade A, Level 1 (78)] and for maintenance treatment to prevent recurrence of depression [Grade A, Level 1A (77)]. Cognitive behaviour therapy (CBT) can be used to treat depression in individuals with depression alone [Grade B, Level 2 (79)] or in combination with antidepressant medication [Grade A, Level 1 (138,184)].

6. Because of the risk of adverse metabolic effects of many antipsychotic medications (especially atypical/second and third generation) [Grade A, Level 1 (37)], regular metabolic monitoring should be performed in people with and without diabetes who are treated with these medications [Grade D, Consensus].

7. Children and adolescents with diabetes should be screened at diagnosis for major depressive disorder [Grade D, Consensus] and regularly for psychosocial difficulties, family distress or mental health disorders [Grade D, Consensus]. An expert in mental health and/or psychosocial issues should provide intervention when required; this individual may be part of the pediatric diabetes health-care team or enlisted by referral [Grade D, Consensus]. Individual and family educational interventions should be included to address stress or diabetes-related conflict when indicated [Grade D, Consensus].

8. Adolescents with type 1 diabetes should be regularly screened using non-judgemental questions about weight and body image concerns, dieting, binge eating and insulin omission for weight loss [Grade D, Level 2 (131)].

Abbreviations:
A1C, glycated hemoglobin; *BMI*, body mass index; *BP*, blood pressure; *CBT*, cognitive behavior therapy; *CV*, cardiovascular; *DKA*, diabetic ketoacidosis; *HR*, hazard ratio; *IFG*, impaired fasting glucose; *LDL-C*, low density lipoprotein; *MDD*, major depressive disorder; *PPD*, postpartum depression; *PTSD*, post-traumatic stress disorder.

Other Relevant Guidelines

Nutrition Therapy, p. S64
Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247

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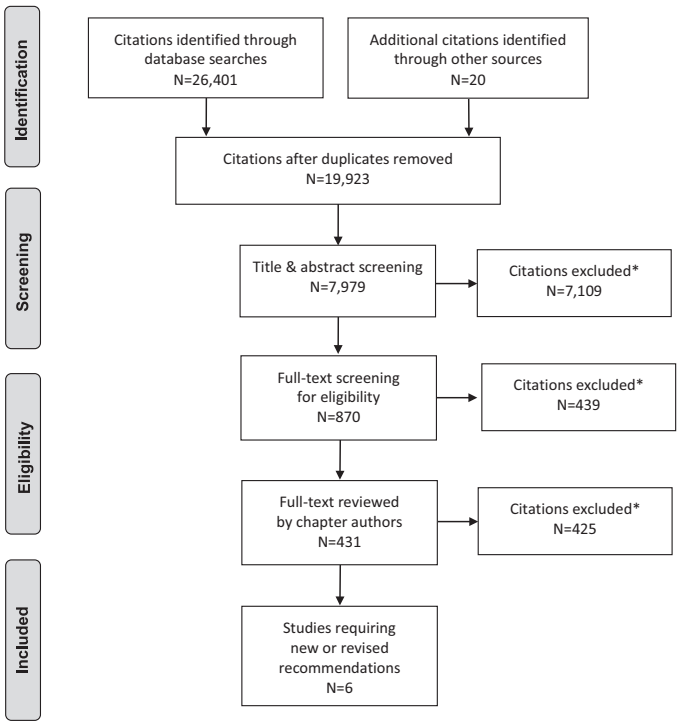
Literature Review Flow Diagram for Chapter 18: Diabetes and Mental Health



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Influenza, Pneumococcal, Hepatitis B and Herpes Zoster Vaccinations

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Influenza vaccination can reduce hospitalization rates by approximately 40% for those individuals deemed to be at high risk.
- Pneumococcal vaccination is desired in people with diabetes as they are considered as likely to be infected as those with other chronic diseases.
- Adults with type 1 and type 2 diabetes are at higher risk of hepatitis B virus infection.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- You should receive routine vaccinations as recommended for anyone with or without diabetes. Check if you are up to date with your vaccinations.
- You should receive:
  - Influenza vaccination("flu shot") every year
  - Pneumococcal vaccination:
    - Initially, when you are over the age of 18 years
    - And, again, when you are over the age of 65 years (if your original vaccination was given when you were younger than 65 years and your last vaccination was over 5 years ago)

Introduction

People with diabetes are considered to be at high risk for morbidity and mortality from influenza and pneumococcal disease (1,2). During recent influenza epidemics, diabetes was considered a significant risk factor for hospitalization (3). Influenza vaccination is associated with up to a 40% risk reduction in mortality (4). Clinical recommendations for vaccination are derived from large cohort studies that included people with diabetes as trials specific to individuals with diabetes are currently lacking. Those with diabetes should receive vaccinations that are recommended for the general population.

Influenza Vaccination in Adults

Data regarding influenza morbidity and mortality in people with diabetes are based on retrospective analyses during influenza epidemics (3–5). A recent epidemiological analysis of pandemic influenza demonstrated that people with diabetes are more likely to be hospitalized or to require intensive care (6). One study demonstrated that, in a Canadian cohort of working-age adults, individuals with diabetes had an increased rate of hospitalizations from influenza-like and pneumonia-influenza illness, as well as all-cause hospitalizations (7). Over a period of 10 influenza seasons, influenza vaccination was shown to be effective in reducing both death and hospitalization from influenza and pneumonia in a cohort that included people with diabetes (8). Two large cohort studies have found that influenza vaccination decreased hospitalizations in both the elderly and working-age adults (9,10).

A Dutch case-control study documented that the incidence of complications was 2 times higher in the unvaccinated group compared to the vaccinated group (11). The rates of hospitalization for influenza, pneumonia, other acute respiratory diseases, myocardial infarction, congestive heart failure, and stroke or diabetes events were reduced by 70%.

Pneumococcal Vaccination in Adults

People with diabetes are at an increased risk of hospitalization for pneumococcal disease (1,12). Prior pneumococcal vaccination is associated with a reduction in death and complications in hospitalized adults with community-acquired pneumonia (13). It is accepted that people with diabetes are at similar risk of developing pneumococcal disease as those with other chronic conditions (1) and, therefore, those with diabetes are encouraged to receive pneumococcal vaccination. Revaccination is recommended as a 1-time event for individuals ≥65 years of age if the original vaccine was given when they were <65 years of age and >5 years earlier. Health Canada recommends vaccination with Pneu-P-23 as more serotypes are included in this vaccine (14).

Some experts suggest a dose of pneumococcal conjugate vaccine followed by Pneu-P-23 vaccine for immunocompetent adults at high risk of pneumonia-influenza disease due to an underlying medical condition, as this may theoretically improve antibody response and immunologic memory (15). If this strategy is chosen, Pneu-C-13 vaccine should be administered first, followed at least 8 weeks later by Pneu-P-23 vaccine. However, Pneu-P-23 vaccine is the vaccine of choice for these individuals. If only 1 vaccine can be provided, it should be Pneu-P-23 vaccine (16).

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends Pneu-P-23 vaccination alone for persons with diabetes aged 19 to 64 years. For people with diabetes ≥65 years or with an immunocompromising condition (e.g. chronic renal failure), they recommend Pneu-C-13 vaccine should be administered first, followed at least 8 weeks later

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by Pneu-P-23 vaccine. In people who have already received Pneu-P-23, at least 1 year should elapse before they are given Pneu-C-13.

Hepatitis B Vaccination

Hepatitis B (HBV) is a highly infectious blood borne pathogen that can lead to acute and chronic liver disease and can be a source of significant morbidity and mortality. HBV infection is the leading cause of hepatocellular carcinoma (HCC), and is the cause of 50% of HCC noted worldwide (17). Hepatitis B and C viruses with *Helicobacter pylori* and human papilloma viruses were responsible for 1.9 million cases of new cancers in 2008, which included liver, gastric and cervical cancers (18). Vaccination against HBV has been effective in reducing childhood HCC and Hepatitis B in Taiwan (19).

Hepatitis B and Diabetes

Adults with type 1 and type 2 diabetes are at higher risk of HBV infection (20). Reilly et al showed that adults between the ages of 23 to 59 years with diabetes were at approximately twice the risk of acute HBV compared with adults without diabetes. People with diabetes can be exposed in many ways to HBV when there is assisted glucose monitoring (20–22). Outbreaks in 2003–2004 of HBV in long-term care homes in the United States, in Mississippi, North Carolina and Los Angeles, prompted an evaluation of HBV in adults with diabetes (22). Infections in these facilities were felt to be due to lack of compliance and implementation of standard hygienic protocols (23). In response, the Hepatitis Vaccines Work Group of the Advisory Committee on Immunization Practices (ACIP) was formed and, based on their findings, HBV vaccination was recommended for those diagnosed with diabetes (24,25). The ACIP report stated that current HBV vaccines are less efficacious and less cost-effective among older adults and recommended that decisions to vaccinate adults with diabetes who are aged >60 years of age incorporate consideration of the person's likelihood of acquiring HBV infection, including the risk posed by an increased need for assisted blood glucose monitoring in long-term care facilities, the likelihood of experiencing chronic sequelae if infected with HBV, and the declining immunologic responses to vaccines that are associated with frailty (24). In Canada, the National Advisory Committee on Immunization recommends HBV vaccine for all children and those in high-risk groups but does not specify individuals with diabetes (14).

Herpes Zoster

The varicella-zoster virus causes 2 distinct syndromes (26). The primary infection syndrome of varicella-zoster presents as varicella (chicken pox). The secondary infection syndrome is the reactivation of the latent varicella-zoster virus in the cranial nerve or dorsal-root ganglia, with spread of the virus along the sensory nerve to the dermatome-termed herpes zoster (26). Herpes zoster are painful blisters or rash, commonly known as shingles. The most common complication of herpes zoster, which persists several months after the lesions have healed, is postherpetic neuralgia pain (27). Complications from herpes zoster can impact significantly on the quality of life for individuals (28).

The annual incidence rate of herpes zoster ranges between 3 to 5 cases per 1000 person-years (29). In Canada, approximately 20% of Canadians are expected to develop herpes zoster at some point in their lives, with an annual report of 130,000 new cases of herpes zoster each year (30). Although the causes of herpes zoster are not fully understood (27), conditions such as inflammatory bowel diseases, diabetes and certain cancerous tumours and leukemias have been associated with an increased risk of herpes zoster (30). The major risk factor for herpes zoster is increased with age. Approximately two-thirds of herpes zoster cases occur in adults 50 years of age and older (27). There is a reduction in cellular immunity during the natural process of aging that predisposes older people to herpes zoster (28). The incidence of herpes zoster also increases substantially in immunocompromised individuals.

Herpes Zoster and Diabetes

Evidence from previous studies has demonstrated that diabetes mellitus is often accompanied by impaired cell-mediated immunity (31). Individuals with diabetes are more prone to infection than individuals without diabetes (32). The clinical evidence regarding diabetes as a risk factor for herpes zoster is scarce. A study conducted by Okamoto et al showed an association between diabetes and herpes zoster (33). Among individuals with diabetes between the ages of 41 to 79 years of age, there was significantly lower cell-mediated immunity to varicella zoster virus compared to the individuals without diabetes (33).

According to the Advisory Committee on Immunization Practices (ACIP) and Canadian Public Health Services (34,35), recommendations for the herpes zoster vaccine are as follows:

- Routinely recommend for adults ≥60 years of age.
- Vaccination before 60 years of age might not have the required protection when the risks and complications of herpes zoster are highest (i.e. ≥60 years of age).
- Protection offered by the herpes zoster vaccine wanes within the first 5 years (36).
- Beyond 5 years of vaccination, duration of protection is uncertain.
- Immunocompromised individuals are an important group to consider when discussing vaccinations, such as herpes zoster vaccine.

RECOMMENDATIONS

1. People with diabetes should receive routine vaccination as recommended for the general population in keeping with the National Advisory Committee on Immunization guidelines [Grade D, Consensus] (available at http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php).

2. People with diabetes should receive an annual influenza vaccination during flu season to reduce the risk of influenza-related hospitalizations and death [Grade C, Level 3 (5)].

3. Pneu-P-23 vaccination should be offered to persons with diabetes aged 19 to 64 years. A 1-time revaccination is recommended for those ≥65 years of age (if the original vaccine was given when they were <65 years of age). For people with diabetes ≥65 years or with an immunocompromising condition (e.g. end stage renal disease), Pneu-C-13 vaccine should be administered first, followed at least 8 weeks later by Pneu-P-23 vaccine. In people who have already received Pneu-P-23, at least 1 year should elapse before they are given Pneu-C-13 [Grade D, Consensus].

Abbreviations:
HBV, hepatitis B; *HCC*, hepatocellular carcinoma.

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Author Disclosures

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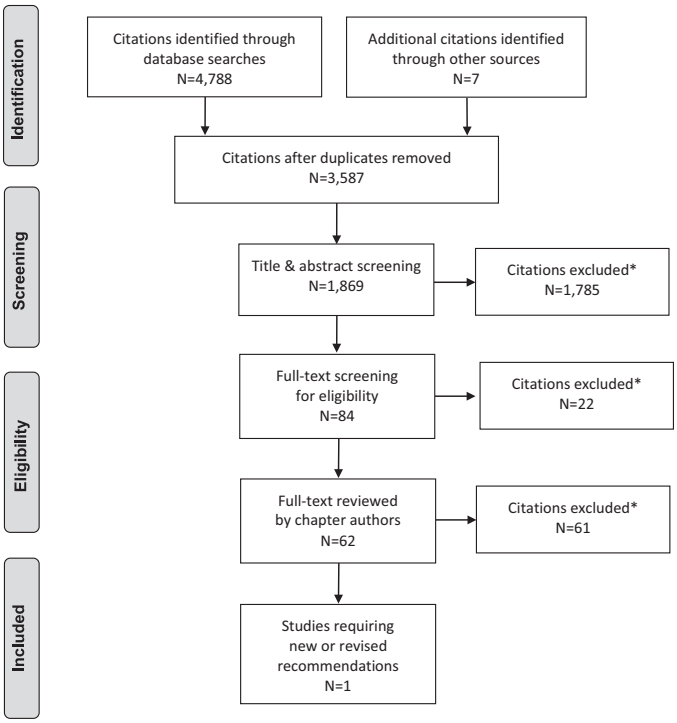
Literature Review Flow Diagram for Chapter 19: Influenza, Pneumococcal, Hepatitis B and Herpes Zoster Vaccinations



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Diabetes and Transplantation

Diabetes Canada Clinical Practice Guidelines Expert Committee

Peter A. Senior MBBS, PhD, FRCP, Mohammed AlMehthel MD, FRCPC, Andrea Miller RN, Breay W. Paty MD, FRCPC

KEY MESSAGES

- For people with diabetes and end stage renal disease, kidney transplantation improves long-term outcomes compared with dialysis.
- For people with type 1 diabetes and end stage renal disease, simultaneous pancreas-kidney transplantation can improve kidney graft survival and result in prolonged insulin independence.
- For people with type 1 diabetes, pancreas or islet allotransplantation improves glycemic control, prevents severe hypoglycemia even in the absence of complete insulin independence, but with the risks of long-term immunosuppression.
- In people undergoing total pancreatectomy for benign pancreatic disease, islet autotransplantation can prevent or ameliorate labile diabetes.
- Post-transplant diabetes is common after solid organ transplantation and is associated with increased risk for mortality, cardiovascular disease and graft loss.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Diabetes sometimes damages kidneys so badly that they no longer work. When kidneys fail, one option is a kidney transplant.
- For certain people with type 1 diabetes, pancreas or islet transplants may help stabilize blood glucose levels.
- Your diabetes health-care team can discuss the benefits and risks of these procedures with you.

Introduction

Restoring endogenous insulin secretion by whole pancreas or islet transplantation has been established as an alternative to insulin injection therapy in select individuals with type 1 diabetes (1,2). Both pancreas and islet transplantation can result in insulin independence and glucose stability, especially in the setting of glucose lability or frequent, severe hypoglycemia. Unfortunately, the absence of prospective randomized controlled trials makes it challenging to draw firm conclusions about the overall efficacy and safety of these therapies compared with exogenous insulin treatment. Also, the limited number of specialized islet and pancreas transplantation centres and the relatively small number of donor pancreases limit the availability of these treatments.

More broadly, diabetes is an important clinical issue in solid organ transplantation. Diabetes is the leading indication for kidney transplants (3) and is a common comorbidity in people listed for other solid organ transplants. New cases of diabetes developing after solid organ transplantation—post-transplant diabetes mellitus (PTDM)—are common and associated with reduced patient and graft survival. There is uncertainty about many aspects of PTDM, including diagnostic criteria, screening, glycemic targets and which glucose-lowering therapies are safest and most effective after transplant (4). Nevertheless, some general recommendations regarding the role of pancreas and islet transplantation, and the diagnosis and management of PTDM, may be made based on a growing body of data and/or current clinical experience.

Pancreas Transplantation

Pancreas transplantation can result in complete independence from exogenous insulin in the majority of cases (5). As shown in Table 1, worldwide, non-controlled 1-, 5- and 10-year mean pancreas graft and patient survival rates differ slightly among the 3 major types of transplantations (6). Long-term pancreas graft survival declines with time, with a median graft survival of 9 years and <10% survival at 21 years (7). Chronic graft failure is the most common reason for transplant loss (8). Glycemic control and glycated hemoglobin (A1C) are markedly improved after successful pancreas transplantation, with most recipients achieving normal glucose tolerance, albeit with hyperinsulinemia (9,10). Improvements in the histological changes of diabetic nephropathy have been reported 5 to 10 years post-transplantation (11,12).

Long-term patient and kidney graft survival improves with simultaneous pancreas kidney (SPK) transplant (13–15). Improvement and/or stabilization of diabetic retinopathy has been demonstrated

Table 1
Reported graft survival rates according to type of pancreas transplantation (6)

Transplant type	1 year	5 year	10 year	15 year
SPK	91.3%	69%	62%	40%
PAK	86%	45%	36%	11%
PTA	85.7%	54%	32%	

PAK, pancreas after kidney; *PTA*, pancreas transplant alone; *SPK*, simultaneous pancreas kidney.

Conflict of interest statements can be found on page S147.

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Table 2
Comparison of beta-cell replacement modalities

	Islet	Pancreas
Outcomes		
Reduce or eliminate hypoglycemia	Yes	Yes
Improve A1C	Yes	Yes
Insulin independence	Yes*	Yes*
Effect on diabetes-related complications		
Microvascular	May be stabilized or improved†	May be stabilized or improved
CV	Not known	May be improved
Risks		
Procedural risks	Minor procedural risk	Major surgical risk
Immunosuppression	Similar agents,‡ life-long immunosuppression	Similar agents,‡ life-long immunosuppression
Other considerations		
ESRD	Consider SIK or IAK	Consider SPK
Functioning renal transplant	Consider IAK if glycemic lability or hypoglycemia§	Consider PAK if glycemic lability or hypoglycemia§

A1C, glycated hemoglobin; *CV*, cardiovascular; *ESRD*, end-stage renal disease; *IAK*, islet after kidney; *PAK*, pancreas after kidney; *SIK*, simultaneous islet and kidney; *SPK*, simultaneous pancreas-kidney.
* More than 1 islet infusion may be required. More reliable and durable insulin independence is more likely with pancreas transplant.
† Retinopathy and neuropathy may be stabilized or improved.
‡ Steroids are avoided in islet transplantation, but may be used in whole pancreas transplantation.
§ No additional risk from immunosuppression.

(16). Peripheral sensory and motor neuropathies also appear to improve after pancreas transplantation (17,18), but these findings are inconsistent and may take years to achieve (19–21). Pancreas transplantation appears to improve cardiovascular (CV) function, carotid intimal medial thickness, blood pressure (BP) and lipid parameters (22–24). Nonrandomized trials suggest a reduction in CV mortality (25,26). Finally, diabetes-related quality of life appears to improve after pancreas transplantation (27).

Islet Transplantation

Islet allotransplantation

Islet allotransplantation involves the infusion of islets isolated from a deceased donor pancreas via the portal vein into the liver (28). Islet transplant alone in people with severe hypoglycemia and impaired awareness of hypoglycemia, despite optimal medical therapy, results in stable, near-normal glycemic control (A1C, glycemic variability) and protection from severe hypoglycemia (29). Similar benefits are seen for islet transplant simultaneously with, or after, kidney transplant compared with intensive insulin therapy (30). Islet transplant usually leads to insulin independence in most recipients, but often requires more than 1 islet infusion (31). Over time, long-term insulin independence rates decline, but recent studies suggest 5-year insulin independence rates up to 60% (32) compared with 10% in early reports (33). Higher proportions maintain long-term graft function, evidenced by sustained secretion of C-peptide, which facilitates improved glycemic control and protection from hypoglycemia despite resuming insulin therapy (29,34,35).

Small, studies suggest stabilization of microvascular complications (36) with islet allotransplantation. Also, successful islet transplantation can improve quality of life (37) and reduces the fear of hypoglycemia (38). Adverse effects of immunosuppressive agents, however, can have a negative impact on quality of life (39).

Risks Associated with Pancreas and Islet Transplantation

Pancreas transplantation represents major abdominal surgery and is associated with significant perioperative risks, including graft thrombosis, hemorrhage, pancreatitis, wound infection, peripancreatic abscesses and duodenal stump leakage (40,41). Islet transplantation is a minimally invasive procedure and is associated with fewer procedural risks, which may include intraperitoneal hemorrhage or branch portal vein thrombosis, but these complications are infrequent at experienced centres (<10% of procedures) and usually self-limited (33,42). Both pancreas and islet transplantation require long-term immunosuppression, which is associated with a number of risks and side effects (43,44). Medication side effects are generally mild and often respond to dose or agent adjustment. Although rare, life-threatening opportunistic infections and malignancies have been reported (42,43). These risks must be carefully weighed against the potential benefits of transplantation for each individual. See Table 2 for a detailed comparison of pancreas vs. islet transplantation.

Islet Autotransplantation after Pancreatectomy

Total pancreatectomy, most commonly performed for chronic painful pancreatitis, often results in labile, insulin-requiring diabetes with a high risk of hypoglycemia. Partial pancreatectomy (e.g. distal pancreatectomy for benign tumours) can also result in diabetes, albeit with a lower risk for hypoglycemia. In both total and partial pancreatectomy for benign pancreatic disease, islets can be isolated from the resected pancreas and returned to the person by infusion into the portal vein or the peritoneal cavity (45,46).

Islet autotransplantation does not require immunosuppression and has minimal additional operative risks. Islet autotransplantation after total pancreatectomy can prevent diabetes with no increase in mortality (47) and can result in durable insulin independence (48). Islet autotransplantation after partial pancreatectomy can also prevent diabetes and provides superior metabolic function, which may be particularly important in subjects at high risk for diabetes (49,50). The metabolic benefits of islet autotransplantation depend on the islet yield, which is generally lower than from deceased donors, but more than 50% of people undergoing total pancreatectomy will have meaningful glycemic benefit (51). Few centres in Canada have facilities to perform islet autotransplantation.

Post-Transplant Diabetes Mellitus—Diagnosis and Treatment

Post-transplant diabetes mellitus (PTDM), previously known as new-onset diabetes after transplantation (NODAT), refers to newly diagnosed diabetes mellitus in a clinically stable person after solid organ transplantation (4). Transient hyperglycemia, which will generally have resolved within 3 months post-transplant is common

and may require short-term treatment (4). Insulin is effective and may be the preferred agent in the acute setting or with marked hyperglycemia. A sensitive and practical method to screen for hyperglycemia in the initial 6-week post-transplant period in people taking corticosteroids is to measure capillary blood glucose (CBG) levels after lunch (i.e. 4 pm) (52).

PTDM is associated with reduced patient and graft survival and increased risk for CVD, infection and other complications of transplant (53). Risk factors for PTDM include recognized risk factors for type 2 diabetes (e.g. age, central obesity, metabolic syndrome, family history of type 2 diabetes), but also some specifically related to transplantation (hepatitis C, cytomegalovirus [CMV], corticosteroid dose, choice of immunosuppressive medications) (53). Pre-transplant screening can identify people at high risk for developing diabetes (54), but is not performed routinely in most transplant centres (4).

PTDM is diagnosed using standard glycemic thresholds (see Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10) when clinically stable (i.e. not in the first 3 months post-transplant) (4). Although the 2-hour oral glucose tolerance test (OGTT) is a more sensitive diagnostic test than A1C, it may be less practical than other methods, but fasting plasma glucose (FPG) is the least sensitive test (55–57). After 3 months post-transplantation, A1C ≥6.5% can be used for diagnosis in stable organ transplant recipients (52,58).

Insulin is a common and effective antihyperglycemic therapy that is often initiated in hospital. While insulin has risks for both hypoglycemia and weight gain, it may be the preferred agent in the acute setting, particularly in the face of high-dose steroids with marked hyperglycemia (see In-Hospital Management of Diabetes chapter, p. S115).

To date, there have been no large trials of antihyperglycemic therapies for the treatment of PTDM. Some small studies have shown efficacy of dipeptidyl peptidase (DPP)-4 inhibitors (59,60) and less weight gain in a small trial vs. insulin glargine (61). However, there is not enough evidence to support specific recommendations regarding choice of antihyperglycemic therapy. Nevertheless, there are a number of issues, which may be considered when selecting glucose lowering therapies, similar to recommendations in the Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88.

Antihyperglycemic agents that do not promote weight gain would generally be preferred since steroids and weight gain are important risk factors for PTDM. Metformin would seem a sensible first-line agent, assuming adequate renal reserve and hepatic function. Adequate renal reserve would be required for a glucagon-like polypeptide (GLP)-1 receptor agonist or sodium-glucose cotransporter-2 (SGLT2) inhibitor to be considered. However, in immunosuppressed patients, the risks of genitourinary infection with SGLT2 inhibitors should be carefully considered (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88).

Insulin secretagogues have risks of hypoglycemia and weight gain, and have inferior durability (which is often attributed to accelerated progression of beta cell decline) (62). Avoiding use of insulin secretagogues in people at increased risk for hypoglycemia (transplant recipients with impaired hepatic or renal function) or in pancreas transplant recipients with graft dysfunction seems prudent.

Transplantation in People with Pre-Existing Diabetes

People with pre-existing diabetes often experience hyperglycemia following transplantation and may need additional antihyperglycemic therapy. Insulin may be required, at least temporarily. No controlled studies have examined treatment strategies for glycemic management after transplantation in people with pre-existing diabetes (4).

RECOMMENDATIONS

1. Individuals with type 1 diabetes and ESRD who are being considered for kidney transplantation should also be considered for simultaneous pancreas-kidney transplantation [Grade C, Level 3 (25,41)].

2. Individuals with type 1 diabetes with inadequate glycemic control characterized by marked glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control and who have a) preserved renal function or b) who have had a successful kidney transplant may be considered for islet allotransplantation [Grade C, Level 3 (29,30)] or pancreas transplantation [Grade C, Level 3 (26) for pancreas after kidney; Grade D, Level 4 (44) for pancreas transplant alone].

3. Individuals undergoing total pancreatectomy for benign pancreatic disease may be considered for islet autotransplantation to prevent the development of diabetes where suitable facilities are accessible [Grade D, Level 4 (47)].

4. Individuals undergoing solid organ transplant should be screened for diabetes and CV risk factors prior to transplant [Grade D, Consensus] and should be screened for PTDM after transplant using:
   a. A1C at 3 months, 12 months and then annually, or with an OGTT if A1C not reliable (see Table 1 in the Monitoring Glycemic Control chapter, p. S47) [Grade C, Level 3 (52,58)]
   b. A 2-hour OGTT or post-lunch capillary blood glucose in the first 3 months after transplant [Grade C, Level 3 (52)].

5. Individuals with PTDM should:
   a. Be treated to individualized glycemic targets [Grade D, Consensus]
   b. Receive healthy behaviour interventions similar to those recommended for people with type 2 diabetes [Grade D, Consensus]
   c. Receive antihyperglycemic agents that do not provoke weight gain, whenever possible, unless contraindicated [Grade D, Consensus]
   d. Avoid insulin secretagogues if they have renal impairment or poorly functioning pancreas transplant [Grade D, Consensus]
   e. Receive insulin for metabolic decompensation or symptomatic/severe hyperglycemia [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *BG*; blood glucose; *BP*, blood pressure; *CBG*; capillary blood glucose; *CV*, cardiovascular; ESRD, end stage renal disease; *FPG*; fasting plasma glucose; *NODAT*, new onset diabetes after transplantation; *OGTT*, oral glucose tolerance test; *PTDM*, post-transplant diabetes mellitus; *SPK* transplant, simultaneous pancreas kidney transplant.

Other Relevant Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S10
Monitoring Glycemic Control, p. S47
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
In-Hospital Management of Diabetes, p. S115

Author Disclosures

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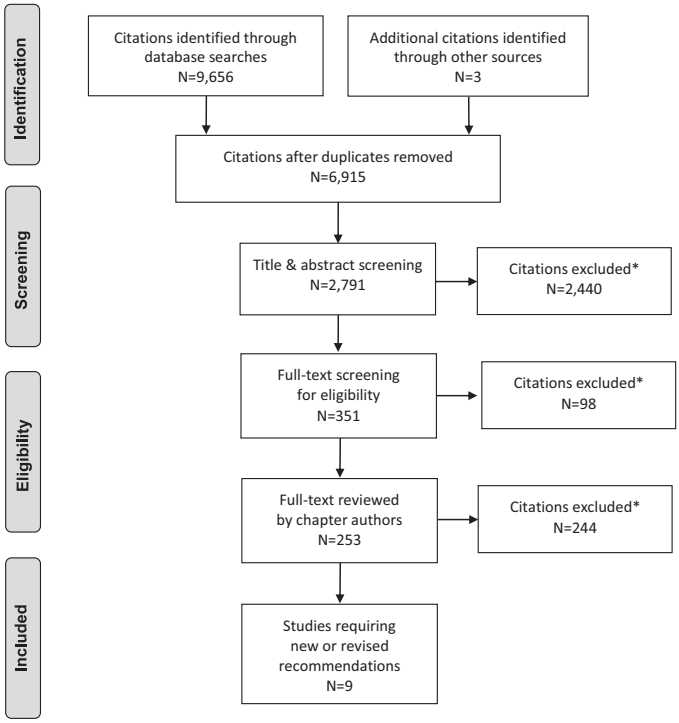
Literature Review Flow Diagram for Chapter 20: Diabetes and Transplantation



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (63).

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2018 Clinical Practice Guidelines

Diabetes and Driving

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The fitness of people with diabetes to drive should be assessed on an individual basis.
- All drivers with diabetes should undergo a medical examination at least every 2 years to assess fitness to drive. Commercial drivers should undergo an assessment at the time of application for a commercial license and as per provincial requirements thereafter.
- People with diabetes should play an active role in assessing their fitness to drive.
- Health-care professionals should educate people with diabetes about strategies to reduce their risks for hypoglycemia while driving. They should also identify and inform individuals with diabetes at higher risk for motor vehicle accidents.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- If you take insulin and/or an insulin secretagogue and intend to drive:
  - Consider measuring your blood glucose level immediately before driving, always keep an emergency supply of fast-acting carbohydrate, such as dextrose tablets, within easy reach inside the vehicle and carry your glucose meter and supplies.
  - Consider measuring your blood glucose level immediately before driving, if you develop symptoms of hypoglycemia, and at least every 4 hours while driving. You can also wear a real-time continuous blood glucose monitoring device.
  - Consider measuring your blood glucose more frequently if there are factors that may increase your risk of hypoglycemia, such as recent physical activity or a delay in eating or skipping a meal.
  - If you have a history of recurrent severe hypoglycemic episodes (i.e. associated with loss of consciousness or needing help from another person) or have hypoglycemia unawareness (lack of early warning symptoms of hypoglycemia, such as tremor, sweatiness and palpitations), you must measure your blood glucose immediately before and at least every 2 hours while driving or wear a real-time continuous blood glucose monitoring device.
  - Do not start driving if your blood glucose level is less than 4 mmol/L. If your blood glucose is less than 4 mmol/L, do not start driving until you have ingested 15 grams of carbohydrate, you have retested and your blood glucose is at least 5 mmol/L. It is suggested to wait for 40 minutes as it takes time for judgment and reflexes to the brain to recover fully from hypoglycemia.
  - If hypoglycemia develops while driving, stop the vehicle in a safe location and remove the keys from the ignition. Treat the low blood glucose and consider waiting 40 minutes before driving.
  - On longer journeys, take regular meals, snacks and periods of rest.
- Immediately notify your health-care provider and your driving licensing body if you experience any episode of severe hypoglycemia while driving or you experience more than 1 episode of severe hypoglycemia while awake but not driving in the past 6 months if you are a private driver, or in the past 12 months if you are a commercial driver.

Introduction

For many Canadians, driving is an essential part of daily living and is often a requirement of employment. Diabetes can affect driving performance because of chronic complications which impair sensory or motor function (retinopathy, neuropathy, amputation, vascular disease), and because of transient cognitive dysfunction or loss of consciousness from antihyperglycemic medication-induced hypoglycemia (primarily related to insulin or insulin secretagogues). In addition, other medical disorders associated with type 2 diabetes, such as sleep apnea, can have an adverse impact on driving performance. As the presence and extent of these factors vary from person to person, the fitness of people with diabetes to drive should be assessed on an individual basis as per provincial regulations.

Driving Risks Associated with Diabetes

Case-control studies have suggested that drivers with diabetes pose a modestly increased but acceptable and measurable risk of motor vehicle accidents compared to drivers without diabetes, but many studies are limited and of poor quality (1,2). Older studies may no longer be as relevant due to changes in road conditions, vehicles and diabetes management (3).

Unrecognized hypoglycemia is the most relevant driving hazard for drivers with diabetes. A number of studies have examined driving performance with a driving simulator during induced hypoglycemia in individuals with type 1 and 2 diabetes (4). Studies in type 1 diabetes have demonstrated that performance starts to deteriorate at blood glucose (BG) levels below 3.8 mmol/L (5,6). In one study, only 30% of drivers self-treated their low BG, and the treatment occurred only when the BG was ≤2.8 mmol/L (5). Fewer than 25% were aware that their driving performance was impaired (5). The ability of deciding when it is safe to drive may be unreliable or absent in those with hypoglycemia unawareness. During a driving simulator

Conflict of interest statements can be found on page S152.

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study, only 4% of those with normal hypoglycemia awareness stated that they would drive while hypoglycemic compared to 43% with impaired awareness of hypoglycemia (5). Studies have demonstrated that cognitive function may not recover until 40 minutes or more after restoration of euglycemia (7–10).

Hypoglycemia is not a problem for drivers with diabetes treated with healthy behaviour interventions (diet and physical activity) alone, nor is it a problem for drivers with diabetes treated with most noninsulin antihyperglycemic medications, when used as monotherapy or in combination with each other. Treatment with insulin secretagogues (sulfonylureas, meglitinides) may provoke higher rates of hypoglycemia when used alone or in combination with other noninsulin antihyperglycemic medications (11), including the elderly (12) (see Hypoglycemia chapter, p. S104; Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88; Diabetes in Older People chapter, p. S283). Studies of rates of motor vehicle accidents in drivers with diabetes have consistently described the highest rates for individuals treated with insulin (12–16).

Factors that have been shown to increase driving risk include previous episodes of severe hypoglycemia within the past 2 years (17–19) with a greater risk in those with lower glycated hemoglobin (A1C) (17,20), previous hypoglycemia while driving (17) and absence of BG monitoring before driving (13,17). Studies have not specifically addressed differences between episodes during waking hours and while asleep. Impaired awareness of hypoglycemia is also a significant risk factor for severe hypoglycemia (19). There is evidence that driving itself is associated with significant metabolic demand and may cause BG to fall (21). These risks may be mitigated by frequent BG testing (22) or use of a real-time continuous glucose monitoring (CGM) device (23). Use of a memory glucose meter is recommended so that measurements can be assessed by the health-care team and by driving authorities, if indicated.

An 11-item questionnaire attempted to identify the at-risk drivers with diabetes (24). Those scoring in the upper quartile reported more driving mishaps than those in the lower quartile. The most discriminating questions regarding accident risk were those that quantified annual mileage, identified a history of hypoglycemia-related vehicle collision, elicited poor self-management of hypoglycemic episodes and screened for the presence of lower limb neuropathy. An Internet-based management program undertaken by drivers with type 1 diabetes reduced the frequency of driving mishaps in high-risk drivers (25).

There are limited data concerning the effects of hyperglycemia on driving, which may depend on how hyperglycemia is defined. In 1 questionnaire-based study, 8% of participants with type 1 diabetes and 40% with type 2 diabetes reported at least 1 episode of disrupted driving associated with hyperglycemia over 1 year (24). No studies have examined the effect of hyperglycemia on driving performance.

Commercial Driving

The risk for commercial vehicle drivers is higher than that for private drivers as the former are on the road many hours of the day or night, thus increasing their time exposure. The consequences of a motor vehicle accident involving a commercial vehicle are also likely to be more serious, particularly if the vehicle carries passengers or dangerous goods. Therefore, higher medical standards are applied for all commercial vehicle drivers (26).

Roles and Responsibilities of the Driver with Diabetes and the Health-Care Provider

People with diabetes should play an active role in assessing their own fitness to drive and should have a duty to report conditions that may potentially impair their ability to drive safely, such as hypoglycemia unawareness and episodes of severe hypoglycemia while driving or while awake but not driving. However, studies have demonstrated limited patient awareness of and adherence to recommendations for safe driving. As few as 15% of adults routinely perform self-monitoring of blood glucose (SMBG) before driving (22,27). A survey in Edinburgh of 202 drivers with insulin-treated diabetes showed only 50% of drivers reported following minimum safe driving recommendations: carrying carbohydrate in the vehicle, measuring glucose before a journey, stopping the vehicle during a hypoglycemic episode and recognizing a low glucose as unsafe to drive (22).

Health-care providers play a critical role in educating people with diabetes on strategies to reduce their risk of hypoglycemia while driving, however, many drivers with diabetes receive little or no advice. In a large multinational study, only 52% of drivers with type 1 diabetes and 27% with type 2 diabetes had discussed driving guidelines with their physician (13). Many health-care professionals have deficiencies in their knowledge about the problems associated with diabetes and driving and how these should be minimized (28). In a Scottish study, only 62% of health-care professionals suggested that insulin-treated drivers should test their blood glucose before driving and 8% did not know that impaired glucose awareness might be a contraindication to driving (27). A study in Finland indicated that among private and commercial drivers treated with insulin with self-reported recurrent severe hypoglycemia, 68% continued to hold a valid driving licence (28).

Mandatory Reporting

Currently, 10 Canadian provinces and territories have a mandatory reporting system obliging legally qualified medical practitioners to report to the appropriate regulatory body those people who have conditions that impair their driving ability (29) (Table 1). Federal organizations, such as the Canadian Council of Motor Transport Administrators (CCMTA), should have consistent, clear and easily accessible reporting mechanisms for physicians and nurse practitioners; in addition, provincial and territorial ministries of transportation should include information on their websites about diabetes and driving, and which types of people with diabetes should be reported. A study in Ontario showed that a program of medical warnings issued to 100,075 people over a 3-year period for a variety of different medical issues, including alcoholism, epilepsy, dementia, sleep disorders and diabetes, resulted in a 45% reduction in

Table 1
Canadian regulations for reporting medically unfit drivers

Province/territory	Reporting*
Alberta	Discretionary
British Columbia	Mandatory (only if the driver has been warned of the dangers of driving and still continues to drive)
Manitoba	Mandatory
New Brunswick	Mandatory
Newfoundland and Labrador	Mandatory
Northwest Territories	Mandatory
Nova Scotia	Discretionary
Nunavut	Mandatory
Ontario	Mandatory
Prince Edward Island	Mandatory
Quebec	Discretionary
Saskatchewan	Mandatory
Yukon	Mandatory

* For more information regarding reporting processes in Canada, see the Canadian Medical Association Driver's Guide available at https://joule.cma.ca/en/evidence/CMA-drivers-guide.html.

annual accident rates when compared with the period before the warning. People with diabetes who received warnings (n=518,104) had a 41% reduction (from 4.49 to 2.71 events per 1,000 patients per year), similar to the total cohort (30).

Mandatory reporting with the goal of optimizing road safety may inadvertently discourage people from discussing their condition with their physician. In the Czech Republic, where physician reporting is mandatory for diabetes, a survey of 663 people found that 52% would conceal or were undecided whether they would report severe hypoglycemic events to their physician (31). A study in the United Kingdom of 2,779 drivers with insulin-treated diabetes for 15 years or more found that 10.5% self-declarations of severe hypoglycemia or impaired awareness of hypoglycemia were inconsistent with their physician's reporting, and resulted in 8.5% of drivers having their license refused (32). Implementation of stricter European Union legislation on driver licensing resulted in a 55% reduction in reported rates of severe hypoglycemia among a cohort of 309 people with type 1 diabetes in Denmark (33).

RECOMMENDATIONS

1. Fitness of people with diabetes to drive should be assessed on an individual basis [Grade D, Consensus]. People with diabetes should take an active role in assessing their ability to drive safely.

2. All drivers with diabetes should undergo a comprehensive medical examination at least every 2 years by a physician/nurse practitioner competent in managing people with diabetes. The medical examination should include an assessment of glycemic control; frequency and severity of hypoglycemia; symptomatic awareness of hypoglycemia; and the presence of retinopathy, neuropathy, nephropathy, amputation and CV disease, to identify whether any of these factors could significantly increase the risk of a motor vehicle accident [Grade D, Consensus]. Commercial drivers should also undergo a medical examination at the time of application for a commercial license [Grade D, Consensus].

3. Drivers with diabetes treated with insulin secretagogues and/or insulin:
   a. Should maintain a log of their SMBG measurements either by using a memory-equipped BG meter or electronic record of BG measurement performed at a frequency deemed appropriate by the person with diabetes and their health-care team. For commercial drivers, for initial commercial licence application, the record should include the last 6 months (or since the diagnosis of diabetes if less than 6 months). BG logs should be verifiable on request [Grade D, Consensus].
   b. Should always have BG monitoring equipment and supplies of rapidly absorbed carbohydrate within easy reach (e.g. attached to the driver's-side visor or in the centre console) [Grade D, Consensus].
   c. Should consider measuring their BG level immediately before and at least every 4 hours while driving or wear a real-time CGM device [Grade D, Consensus].
   d. Should not drive when their BG level is <4.0 mmol/L [Grade C, Level 3 (5) for type 1 diabetes; Grade D, Consensus for type 2 diabetes]. If the BG level is <4.0 mmol/L, they should not drive until at least 40 minutes after successful treatment of hypoglycemia has increased their BG level to at least 5.0 mmol/L [Grade C, Level 3 (10) for type 1 diabetes; Grade D, Consensus for type 2 diabetes].
   e. Must refrain from driving immediately if they experience severe hypoglycemia while driving, and notify their health-care provider as soon as possible (no longer than 72 hours) [Grade D, Consensus].

4. Private and commercial drivers with diabetes and hypoglycemia unawareness or history of severe hypoglycemia in the past 12 months **must** measure their BG level immediately before and at least every 2 hours while driving or wear a real-time CGM device [Grade D, Consensus].

5. If any of the following occur, health-care professionals should inform people with diabetes treated with insulin secretagogues and/or insulin to no longer drive, and should report their concerns about the person's fitness to drive to the appropriate driving licensing body:
   a. Any episode of severe hypoglycemia while driving in the past 12 months [Grade D, Consensus].
   b. More than 1 episode of severe hypoglycemia while awake but not driving in the past 6 months for private drivers, and in the past 12 months for commercial drivers [Grade D, Consensus].

Abbreviations:
BG, blood glucose; *CBG*, capillary blood glucose; *CGM*, continuous glucose monitoring; *SMBG*, self-monitoring of blood glucose.

Other Relevant Guidelines

Monitoring Glycemic Control, p. S47
Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Hypoglycemia, p. S104
Diabetes in Older People, p. S283

Relevant Appendix

Appendix 10. Sample Diabetes and Driving Assessment Form

Author Disclosures

Dr. Houlden reports grants from Boehringer Ingelheim, Novo Nordisk, and Eli Lilly, outside the submitted work. Lori Berard has received consulting and/or speaker fees from Bayer, Boehringer Ingelheim, Sanofi, Eli Lilly, Novo Nordisk, Janssen, AstraZeneca, and Merck. Dr. Yale reports grants and personal fees from Eli Lilly Canada, Sanofi, Merck, AstraZeneca, Boehringer Ingelheim, Janssen, and Medtronic; personal fees from Novo Nordisk, Takeda, Abbott, and Bayer; and grants from Mylan, during the conduct of the study. No other authors have anything to disclose.

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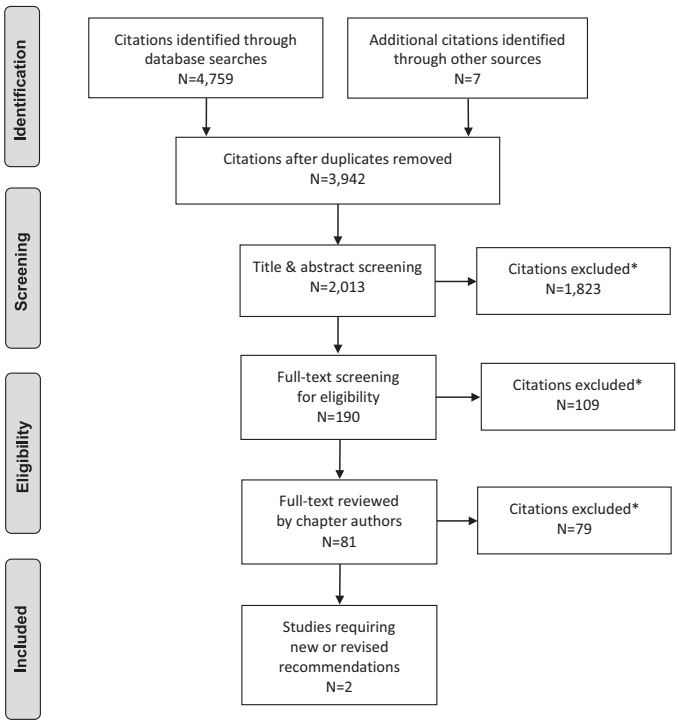
Literature Review Flow Diagram for Chapter 21: Diabetes and Driving



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (34).

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2018 Clinical Practice Guidelines

Complementary and Alternative Medicine for Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Anywhere from 25% to 57% of people with diabetes report using complementary or alternative medicine.
- Some natural health products have shown a lowering of A1C by ≥0.5% in trials lasting at least 3 months in adults with type 2 diabetes, but most are single, small trials that require further large-scale evaluations before they can be recommended for widespread use in diabetes.
- A few more commonly used natural health products for diabetes have been studied in larger randomized controlled trials and/or meta-analyses refuting the popular belief of benefit of these compounds.
- Health-care providers should always ask about the use of complementary and alternative medicine as some may result in unexpected side effects and/or interactions with traditional pharmacotherapies.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Many people with diabetes use complementary medicine (along with) or alternative medicine (instead of) with conventional medications for diabetes.
- Although some of these therapies may have the potential to be effective, they have not been sufficiently studied and others can be ineffective or even harmful.
- It is important to let your health-care providers know if you are using complementary and/or alternative medicine for your diabetes.

Introduction

Despite advances in the management of type 1 and type 2 diabetes, therapeutic targets are often not met. People dissatisfied with conventional medicine often turn to nontraditional alternatives. Complementary and alternative medicine (CAM) can be loosely defined as health-care approaches developed outside of mainstream Western, or conventional medicine, with "complementary" meaning used together with, and "alternative" meaning used in place of conventional medicine (1). According to a report from the Fraser Institute, 50% to 79% of Canadians had used at least 1 CAM sometime in their lives, based on surveys from 1997, 2006 and 2016 (2). The most common types used in 2016 were massage (44%), chiropractic care (42%), yoga (27%), relaxation techniques (25%) and acupuncture (22%). According to the United States 2012 National Health Interview Survey (NHIS), 17.7% of American adults used a dietary supplement other than vitamins and minerals (3). A few surveys have sought to characterize the use of CAM in persons with diabetes. In a Canadian study of 502 people with diabetes, 44% were taking over-the-counter supplements with 31% taking alternative medications (4). A United States national survey reported 57% of those with diabetes using CAM in the previous year (5). The Medical Expenditure Panel Surveys (MEPS) showed that those with diabetes were 1.6 times more likely to use CAM than those without diabetes, with older age (≥65 years) and higher educational attainment (high school education or higher) independently associated with CAM use (6). An Australian study reported 25% of people with diabetes stated they had used CAM within the previous 5 years (7).

This chapter will review CAM, including natural health products (NHP) and others, such as yoga, acupuncture, tai chi and reflexology, that have been studied for the prevention and treatment of diabetes and its complications.

NHP for the Prevention and Treatment of Diabetes and Its Complications

In Canada, NHP are defined as vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines, such as traditional Chinese medicines, probiotics, and other products like amino acids and essential fatty acids (8). They are regulated under the Natural Health Products Regulations, which came into effect in 2004. In general, the current level of evidence for the efficacy and safety of NHP in people with diabetes is lower than that for pharmaceutical agents. Trials tend to be of shorter duration and involve smaller sample sizes. Concerns remain about standardization and purity of available compounds, including their contamination with regular medications and, in some cases, toxic substances (9–11). Various NHP have been studied to evaluate their impact on the development of both type 1 and type 2 diabetes, glycemic control in people with diabetes, and on the various complications of diabetes.

NHP for the Prevention and Treatment of Diabetes

A number of immune modulators have been studied in an attempt to prevent or arrest beta cell decline in type 1 diabetes, most with limited success. A few NHP have also been studied in this

Conflict of interest statements can be found on page S157.

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regard. A randomized controlled trial of people with new-onset type 1 diabetes assessed the effect of vitamin D supplementation on regulatory T (Treg) cells (12). After 12 months, Treg suppressive capacity was improved, although there was no significant reduction in C-peptide decline. Observational studies have suggested an inverse relationship between vitamin D levels and the development of type 2 diabetes (13), although randomized controlled trials are lacking (14). In the large, prospective cohort study, The Environmental Determinants of Diabetes in the Young (TEDDY), early probiotic supplementation may reduce the risk of islet autoimmunity in children at the highest genetic risk of type 1 diabetes (15).

A number of NHP have been evaluated to assess their effect on the progression from impaired glucose tolerance (IGT) to diabetes. Tianqi is a traditional Chinese medicine consisting of 10 different herbs. In a double-blind, placebo-controlled trial of 12 months duration, Tianqi was shown to reduce the progression from IGT to type 2 diabetes by 32% (16). A systematic review and meta-analysis of observational studies of omega-3 fatty acids or fish intake showed that an increased intake of alpha linoleic acid (ALA) and fatty fish reduced the risk of type 2 diabetes significantly with ALA, only in Asians (17). In a randomized controlled trial, the traditional Chinese medicine Shenzhu Tiaopi granule (SZTP) significantly reduced the conversion from IGT to type 2 diabetes to 8.52% from 15.28% with placebo, with a significantly higher number of people with IGT reverting to normal blood glucose levels as well (42.15% vs. 32.87% for placebo) (18).

In adults with type 2 diabetes, the following NHP have been shown to lower glycated hemoglobin (A1C) by at least 0.5% in randomized controlled trials lasting at least 3 months:

- Ayurveda polyherbal formulation (19)
- *Citrullus colocynthis* (20)
- *Coccinia cordifolia* (21)
- Eicosapentaenoic acid (22)
- *Ganoderma lucidum* (23)
- Ginger (*Zingiber officinale*) (24)
- *Gynostemma pentaphyllum* (25)
- *Hintonia latiflora* (26)
- Lichen genus *Cladonia* BAFS “Yagel-Detox” (27)
- Marine collagen peptides (28)
- Nettle (*Urtica dioica*) (29)
- Oral aloe vera (10)
- *Pterocarpus marsupium* (vijayasar) (30)
- *Salacia reticulata* (31)
- *Scoparia dulcis* porridge (32)
- Silymarin (33,34)
- Soybean-derived pinitol extract (35)
- Touchi soybean extract (36)
- Traditional Chinese medicine herbs:
  - Berberine (37)
  - Fructus Mume (38)
  - Gegen Qinlian Decoction (GQD) (39)
  - Jianyutangkang (JYTK) with metformin (40)
  - Jinlida with metformin (41)
  - Sancaijiangtang (42)
  - Shen-Qi-Formula (SQF) with insulin (43)
  - Tang-Min-Ling-Wan (TM81) (44)
  - Xiaoke (contains glyburide) (11)
  - Zishentongluo (ZSTL) (45)
- *Trigonella foenum-graecum* (fenugreek) (46,47)

These products are promising and merit consideration and further research, but, as they are mostly single, small trials or meta-analyses of such, it is premature to recommend their widespread use.

The following NHP either failed to lower A1C by 0.5% in trials lasting at least 3 months in adults with type 2 diabetes, or were studied in trials of shorter duration, nonrandomized or uncontrolled:

- *Agaricus blazei* (48)
- American ginseng (*Panax quinquefolius* L.) (49)
- Antioxidants: (fruit/vegetable extract) (50), (pomegranate extract) (51)
- *Camellia sinensis* (52)
- Flaxseed oil (53)
- French maritime pine bark (54)
- Ginseng (55,56)
- *Juglans regia* extract (57)
- Liuwei Dihuang Pills (LDP) (58)
- *Momordica charantia* (bitter melon or bitter gourd) (59,60)
- *Rosa canina* L. (rose hip) (61)
- *Salvia officinalis* (62)
- Soy phytoestrogens (63)
- *Tinospora cordifolia* (64)
- *Tinospora crispa* (65)
- Vitamin C (66–68)
- Vitamin E (69–73)

The following NHP have demonstrated conflicting effects on A1C in trials lasting at least 3 months in adults with type 2 diabetes:

- Cinnamon (74–79)
- Coenzyme Q10 (80–83,85,86)
- *Ipomoea batatas* (caiapo) (87,88)
- L-carnitine (89–92)
- Magnesium (93–99)
- Omega 3 fatty acids (100,101)
- Probiotics (102,103)
- Zinc (104,105)

A few products, such as chromium, vitamin D and vanadium, have been the subjects of special interest in diabetes.

Chromium is an essential trace element involved in glucose and lipid metabolism. Early studies revealed that chromium deficiency could lead to IGT, which was reversible with chromium repletion. This led to a hypothesis that chromium supplementation, in those with both adequate and deficient chromium stores, could lead to improved glucose control in people with diabetes (106,107). Indeed, an analysis of the large NHANES database showed that, in those in the general population who reported consuming a chromium supplement, the odds of developing diabetes was 19% to 27% lower than those not taking a chromium supplement (108). However, randomized controlled studies of chromium supplementation have had conflicting results, with most showing no benefit on improving A1C (109–121), although some showed an improved fasting glucose level (120,121). Most were small studies, of short duration, and some not double-blinded. More recent meta-analyses have also reported conflicting results, with some concluding no benefit of chromium on reducing A1C, lipids or body weight in people with diabetes (122), and others reporting some benefit depending upon the dose and formulation consumed (84). The later meta-analysis reported marked heterogeneity and publication bias in the included studies.

Vitamin D has received much interest recently with purported benefits on cardiovascular disease (CVD), cancer and diabetes. Randomized controlled trials have not demonstrated a benefit of vitamin D supplementation on glycemic control in diabetes (123–138), further confirmed by meta-analyses (139,140).

Vanadium, a trace element that is commonly used to treat type 2 diabetes, has not been studied in randomized controlled trials evaluating glycemic control by A1C over a period of 3 months or longer.

NHP for the Treatment of the Co-Morbidities and Complications of Diabetes

A number of NHP have been evaluated for the various co-morbidities and complications of diabetes, including lipids and blood pressure (BP) in diabetes, as well as CVD, nephropathy, retinopathy and peripheral neuropathy. As with the studies of glycemic control, most had small sample sizes and meta-analyses had marked heterogeneity of included studies, making strong conclusions difficult.

Randomized controlled trials demonstrating a benefit on lipid parameters in diabetes include: Ayurvedic polyherbal formulation (19), Hintonia latiflora (26) and magnesium (99). In postmenopausal women with type 2 diabetes, vitamin D supplementation for 6 months reduced serum triglycerides (TG) without effect on other lipid parameters (141), while a meta-analysis with high heterogeneity showed benefit on lowering total cholesterol and TG (142). Other studies have failed to show significant benefit of vitamin D supplementation on lipids in people with diabetes (130,137,143). A meta-analysis of Berberine showed it to reduce TG and increase high-density lipoprotein cholesterol (HDL-C) more than traditional lipid-lowering drugs, with no difference on total or low-density lipoprotein cholesterol (LDL-C) (37). Berberine was also shown to reduce total and LDL-C and increase HDL-C combined with traditional lipid-lowering drugs compared with those drugs alone.

Randomized controlled trials demonstrating a benefit on systolic and/or diastolic BP include: magnesium (99), American ginseng (*Panax quinquefolius* L.) (49) and Purslane extract (*Portulaca oleracea* L.) (144). Berberine when combined with traditional BP medications can lower systolic BP by an additional 4.9 mmHg and diastolic BP by 2 mmHg, but not when compared with traditional antihypertensive medications alone (37). In 1 meta-analysis, vitamin D was shown to reduce BP by a statistically significant, but not clinically meaningful amount (145).

Ethylene diamine tetra-acetic (EDTA) acid chelation therapy has been postulated to have a number of cardiovascular (CV) benefits. A large randomized controlled trial (Trial to Assess Chelation Therapy—TACT) showed a modest benefit of an 18% risk reduction for a composite of CV complications in people with a recent myocardial infarct (146). A pre-specified subanalysis of people with diabetes showed a more robust 39% to 41% risk reduction in the primary endpoint out to 5-years follow up (147).

The traditional Chinese medicine product, The Compound Danshen Dripping Pill (CDDP), consisting of 3 herbal preparations, was evaluated in a randomized controlled trial of 24 weeks duration, for its effect on the progression of diabetic retinopathy (148). Using a nonstandardized method of grading fluorescence fundal angiography, higher doses of CDDP were found to delay the progression of diabetic retinopathy.

A number of NHP have been reported to improve diabetic nephropathy. However, there is variation in the definition of diabetic nephropathy in the various studies, with many assessing urinary albumin excretion (UAE) and/or 24-hour urine protein excretion without a confirmatory diagnosis. Many are of short duration, some without reporting an assessment of renal function or its progression, or with conflicting results on the various measures. Some products showing a reduction in UAE in people with diabetes include: the traditional Chinese medicines Yiqi Huayu, Yiqi Yangyin (149), Qidan Dihuang Grain (150), and Jiangzhuo (SKC-YJ) (151), Huangshukuihua (Flos Abelmoschi Manihot) (152,153), Pueraria lobata (gegen, puerarin) (154), Tangshen Formula (155), Zishentongluo (ZSTL) (45), vitamin D (156), and vitamin D analogue paricalcitol in type 1 diabetes (157).

A number of NHP have been reported to improve diabetic peripheral neuropathy, as assessed by pain scores and/or nerve conduction studies (NCS). Topical Citrullus colocynthis (bitter apple) extract oil was studied in a small randomized controlled trial in people with painful diabetic polyneuropathy (158). After 3 months, there was a significantly greater decrease in mean pain score and improvement in nerve conduction velocities compared with placebo. A meta-analysis of puerarin in diabetic peripheral neuropathy reported benefits in pain scores and NCS (159). In a small randomized controlled trial, the traditional Chinese medicine MHGWT showed reduced pain scores compared with placebo after 12 weeks of treatment (160).

A number of the above and other NHP have been evaluated for their effects on various pre-clinical parameters, biomarkers and surrogate clinical markers involved in the pathogenesis of diabetes and its complications. A discussion of these papers is beyond the scope of this chapter.

Adverse Effects

It is important to consider potential harm from the use of NHP. A number of studies of NHP report adverse events, such as gastrointestinal (Fenugreek, Berberine, TM81, bitter melon, oral aloe vera) and dizziness (JYTK). In 1 trial of Tinospora crispa, hepatotoxicity was seen in 2 participants (65). Large doses of Citrullus colocyn can induce diarrhea, but no side effects were reported in the lower doses used in 1 trial (20). Momordica charantia, an NHP commonly used for glycemic control, is an abortifacient (161). Most clinical trials have evaluated small sample sizes over relatively short periods of time and, thus, may not identify all potential side effects or risks.

Some NHP contain pharmaceutical ingredients and/or properties. The Xiaoke Pill contains glibenclamide (glyburide) (11). Nettle has insulin secretagogue, peroxisome proliferator-activated receptor (PPAR) and alpha-glucosidase activities. Only NHPs that are properly labelled with a valid natural product number (NPN) should be used to avoid adulteration with unlabelled pharmaceuticals or other contaminants.

Drug-herb interactions may also occur. The most well described is Hypericum perforatum (St. John's wort), which can affect the metabolism of many drugs, including statins, by inducing cytochrome P450 3A4 (CYP3A4). Some studies have reported poorer glycemic control in people using glucosamine sulfate for osteoarthritis, but a systematic review concluded that the evidence does not support this concern (162).

Other Complementary and Alternative Approaches for the Prevention and Treatment of Diabetes and Its Complications

A number of complementary and alternative approaches have been studied to some degree for diabetes and its complications, others have not. Included here are studies of yoga, traditional Chinese medicine and reflexology. Other modalities of CAM, such as chiropractic or osteopathic manipulation, homeopathy, shiatsu, registered massage therapy or craniosacral therapy do not have studies specific to diabetes.

Yoga

The Sanskrit definition of yoga means union or connection. Yoga is a Hindu spiritual discipline. There are many types of yoga, each with its own techniques and methods to awaken greater awareness and connection to self and life. Most practices of yoga include a series of physical postures, breathing and meditation for health, relaxation and overall well-being. Yoga or yoga therapy is often included in a holistic practitioner's (chiropractor, naturopath,

osteopath, shiatsu therapist) plan of management for stress reduction and physical strengthening.

Studies of yoga in the management of people with type 2 diabetes show some benefit on glycemic control, lipids and BP, although published studies are generally of short duration with small numbers. In a systematic review and meta-analysis, yoga was found to have positive effects on reducing A1C, as well as fasting and postprandial glucose values (163). There was high heterogeneity among the studies included in the analysis. Other systematic reviews and meta-analyses showed similar improvements in glycemic parameters, as well as improvements in the lipid profile and BP, with similar limitations in the individual studies included (164,165) (see Physical Activity and Diabetes chapter, p. S54). In a meta-analysis of smaller studies looking at comparing the effectiveness of the leisure activities yoga, walking and tai chi on glycemic control in people with type 2 diabetes, yoga with regular frequency (3 times a week) was shown to be more effective than tai chi or walking in lowering A1C levels (166).

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) encompasses a holistic system that includes the combination of herbal medicines, acupuncture, tui na (rigorous massage), dietary therapy, qi gong and tai chi (mind/body techniques combining breathing, movement and mental focus). TCM works within a different paradigm than Western Medicine and, as such, can be difficult to study by Western research techniques. Treatments are complex and focused on individual imbalances detected by pulse and tongue diagnosis rather than specific diseases. Most research on the effectiveness of TCM for people with diabetes is based on specific techniques or Chinese herbal remedies as reviewed above.

Acupuncture is a branch of TCM involving the stimulation of specific points along energy meridians throughout the body to either sedate or tonify the flow of energy. There are various techniques of acupuncture, such as electro and laser acupuncture, and different systems of acupuncture, including scalp and auricular acupuncture. The system and technique most commonly referred to and most often studied refers to the technique of penetrating the skin at specific acupuncture points with thin solid metal needles that are manipulated by the hands.

Acupuncture has not been shown to improve A1C in people with diabetes, with 1 small randomized controlled trial showing it to be no different than placebo on FPG and oral glucose tolerance testing (OGTT) (167). A meta-analysis of acupuncture for diabetic gastroparesis concluded that acupuncture improved some dyspeptic symptoms, such as nausea, vomiting, loss of appetite and stomach fullness, with no improvement in solid gastric emptying (168). A systematic review of randomized controlled trials of manual acupuncture for the treatment of diabetic peripheral neuropathy reported that manual acupuncture had a better effect on global symptom improvement compared with vitamin B12 or no treatment, and that the combination of manual acupuncture and vitamin B12 had a better effect compared with vitamin B12 alone. However, the authors could not draw clinically relevant conclusions because of high risks of bias in the studies included (169).

Tai chi is an ancient mind and body practice involving gentle, slow, continuous body movements with mental focus, breathing and relaxation. Although there may be some benefit in quality of life, there is little evidence for benefit of tai chi on glycemic control in diabetes (170,171).

Manual Therapies

There is a growing number of people with diabetes who seek care for musculoskeletal complaints and overall lifestyle management from natural and/or complementary medicine practitioners. Manual therapies, including chiropractic, physiotherapy, shiatsu, registered massage therapy and craniosacral therapy have no randomized controlled trial data in people with diabetes. A few small studies on tactile massage, a superficial gentle form of massage, have failed to demonstrate a significant beneficial effect on A1C (172–174). Reflexology is a system of massage based on the theory that reflex points on the feet, hands and head are linked to other internal parts of the body. In a small, open-label, randomized controlled trial in people with diabetic peripheral neuropathy, foot reflexology was shown to reduce A1C and FPG, and improve pain scores and nerve conduction velocity (175).

RECOMMENDATIONS

1. Health-care providers should ask about the use of complementary and alternative medicine in people with diabetes [Grade D, Consensus].

2. There is insufficient evidence to make a recommendation regarding efficacy and safety of complementary or alternative medicine for individuals with diabetes [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *ALA*, alpha linoleic acid; *BP*, blood pressure; *CAM*, complementary or alternative medicine; *CV*, cardiovascular; *CVD*, cardiovascular disease; *FPG*, fasting plasma glucose; *HDL-C*, high-density lipoprotein cholesterol; *IGT*, impaired glucose tolerance; *LDL-C*, low-density lipoprotein cholesterol; *MI*, myocardial infarct; *NCS*, nerve conduction studies; *NHP*, natural health product; *NPN*, natural product number; *OGTT*, oral glucose tolerance test; *TCM*, traditional Chinese medicine; *TG*, triglycerides, *UAE*, urinary albumin excretion.

Other Relevant Guidelines

Physical Activity and Diabetes, p. S54

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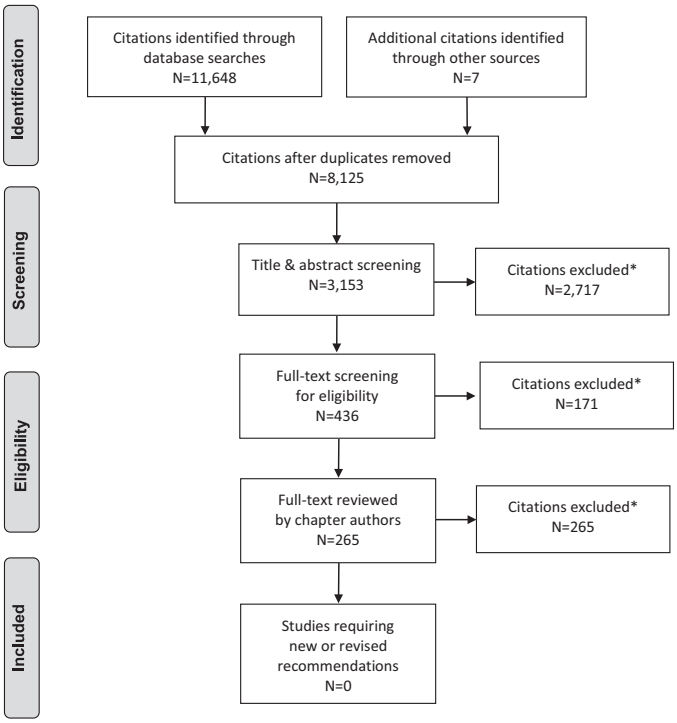
Literature Review Flow Diagram for Chapter 22: Complementary and Alternative Medicine for Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Cardiovascular Protection in People With Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes significantly accelerates the development and natural history of cardiovascular disease compared to individuals without diabetes.
- Healthy behaviour interventions and pharmacological approaches aimed at cardiovascular disease risk reduction can significantly reduce morbidity and mortality, and are an important cornerstone of the management of diabetes.
- Although young people with diabetes rarely have a high proximate (<10 year) risk for cardiovascular disease events, they have a relative proximate risk manyfold greater than individuals of similar age without diabetes.
- Historically, pharmacological cardiovascular protection approaches have focused on low-density lipoprotein cholesterol and blood pressure reduction, and have demonstrated significant and clinically meaningful cardiovascular risk reduction. Recent data have indicated that certain antihyperglycemic agents are also cardioprotective.
- The requirement for pharmacological cardiovascular protection therapies (statins, angiotensin-converting enzyme inhibitors or aldosterone receptor blockers, and anti-platelets) should consider both an individual's proximate and lifetime cardiovascular disease event risk.
- There is emerging recognition that nonatherothrombotic cardiovascular disease complications, such as heart failure, are an important cause of morbidity and mortality in diabetes.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Ask your doctor about the ABCDEs to reduce your risk of heart attack and stroke:
  - **A** = A1C – Blood glucose control. The target is usually 7.0% or less.
  - **B** = BP – Blood pressure control (less than 130/80 mmHg).
  - **C** = Cholesterol – LDL-cholesterol less than 2.0 mmol/L. Your physician/nurse practitioner may advise you to start cholesterol-lowering medication.
  - **D** = Drugs to protect your heart – These include blood pressure pills (ACE inhibitors or ARBs), cholesterol-lowering medication ("statins"), and, in people with existing cardiovascular disease, certain blood glucose lowering medications. These blood glucose-lowering medications can protect your heart even if your blood pressure and/or LDL-cholesterol are already at target.
  - **E** = Exercise/Eating — Regular physical activity, which includes healthy eating, and achievement and maintenance of a healthy body weight.
  - **S** = Stop smoking and manage stress.

Introduction

Of the many complex complications of diabetes, adverse cardiovascular (CV) events have the greatest capacity to cause sudden or premature death and devastating disability. Myocardial infarction (MI), stroke and amputation are all manifestations of the aggressive atherosclerosis that can occur with diabetes. However, not every person with diabetes is at equal risk for CV atherosclerotic events and not everyone will benefit equally from healthy behaviour and pharmacological interventions intended to reduce cardiovascular disease (CVD) event risk. Over the last 2 decades, strong evidence has continued to accumulate that the CV risks of diabetes can be reduced significantly through comprehensive and treatment target-driven risk factor modification (1–5). There is also growing appreciation that, in addition to atherothrombotic consequences, other CV disorders, such as heart failure, are an important cause of morbidity and mortality in diabetes.

Determining CVD Event Risk

People with diabetes are clearly at increased risk of premature morbidity and mortality related to CVD (6). Diabetes confers a CVD event risk that is equivalent to aging approximately 15 years, with a transition from intermediate to high risk in men at age 47.9 years, and in women at 54.3 years (6). The term "vascular age" refers to models of CVD event risk that predict an individual's CVD event risk and compare the event risk to age-adjusted CVD event risk. Vascular age is a primary determinant in both proximate (<10 years) and lifetime risk of adverse CVD events. In people with diabetes with low-to-normal levels of blood pressure (BP), low-density lipoprotein cholesterol (LDL-C) and blood glucose (BG), chronological age and vascular age are usually in close continuity. However, in the presence of elevated levels of those same variables, together with smoking and physical inactivity, vascular age accelerates far more rapidly than chronological age.

As a powerful catalyst of vascular inflammation, diabetes is the disease state that accelerates vascular age at the greatest rate. Thus, the use of pharmacotherapy for CVD risk factor reduction in younger persons with diabetes who are not at a high proximate risk but, as a consequence of their diabetes, have a steep CVD event risk trajectory, can be justified by the potentially substantial long-term benefits of earlier and lifelong therapy (3–5,7,8).

Conflict of interest statements can be found on page S167.

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Traditional CVD event risk models predict an individual's proximate CVD event risk based on risk factors, such as diabetes, hypertension, serum lipids and smoking. These models discriminate poorly between higher- and lower-risk populations, particularly for younger individuals (9–12). In addition, no current CVD event risk model can reliably exclude people with diabetes who are unlikely to benefit from long-term CV protection strategies given the well-documented lifetime risk of CVD events. As a result, far in advance of the appearance of CV symptomatology, most people with diabetes are very likely to benefit from CVD risk factor reduction and the adoption of healthy behaviours (3–5,7,8).

Cardiovascular Protection

The phrase "vascular protection" was originally coined in recognition of the apparent ability of some pharmacologic interventions to evoke greater reductions in the incidence of CVD events than would have been predicted based on their separate direct effects on the risk factors for atherosclerosis (13). This putative protective effect has been attributed to the enhancement of vascular endothelial functions that inhibit thrombosis, suppress macrophage and monocyte adherence to the endothelium, and minimize oxidative stress at the level of the endothelium (14). Over time, the protective effect from adverse CVD events has also been extended to comprehensive healthy behaviour interventions and simultaneous multifactorial atherosclerosis risk factor reductions, such that the whole in CV protection is indeed greater than the sum of the parts (3–5). The mechanistic explanation for why multifaceted CV protection interventions are multiplicative, rather than simply additive, is almost certainly related to, but not necessarily limited to, their favourable modulation of the pro-inflammatory, pro-thrombotic and pro-proliferative atherosclerotic vascular environment in diabetes.

In the STENO-2 Trial, a very small number of participants with type 2 diabetes (n=160) were randomized to usual care or a program of comprehensive healthy behaviour interventions (smoking cessation, weight management, physical activity) and the treatment target-driven pharmacological therapy of BP and serum lipids (3,4). Despite the very small number of participants, there was a 53% relative risk reduction in major adverse cardiac events (MACE) and a 20% absolute risk reduction after 13 years of follow up. The number needed to treat (NNT) for mortality reduction was a mere 5 persons. More recently, data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study have demonstrated that, following cardiac revascularization, participants who had their CVD risk factors controlled benefited from significantly improved CVD morbidity and mortality over 5 years of follow up (5). Similarly, in a population-based observational study of 867 newly diagnosed individuals with diabetes, the relative risk of MACE was increased over 4-fold during 5 years of follow up for those persons who adopted no healthy behaviour changes vs. those who adopted either 3 or 4 healthy behaviours (15).

Although the number of participants in these trials is relatively small compared to those in randomized trials of pharmacological agents, the data suggest that efficacious CV protection can be achieved through a combination of healthy behaviours and pharmacologic treatment of CVD risk factors to achieve the targets recommended by evidence-informed clinical practice guidelines (16). Therefore, all people with diabetes should receive a comprehensive, multifactorial strategy to reduce CVD event risk.

Strategies for CV Protection

In 1 prospective cohort study of 867 people with newly diagnosed diabetes aged 40 to 69 years, CVD risk was inversely associated with the number of healthy behaviour changes adopted in the year after the diagnosis of diabetes (15). The CV protection benefits of each of the healthy behaviour interventions discussed below can be attributed to their significant anti-inflammatory, antithrombotic and anti-proliferative effects (17).

Smoking cessation

In individuals with diabetes, smoking is an independent risk factor for all-cause mortality. It increases the risk of MI 1.4-fold, stroke by 30% (18), and progression to end stage renal disease (ESRD) (19); and is associated with poorer glycemic control. Quitting smoking has been shown to reduce CV risk in people with diabetes (20).

Physical activity

In several randomized trials, exercise has been shown to improve CV risk factors (dyslipidemia, BP and body composition) in people with type 2 diabetes (21). However, no clinical trials have demonstrated a reduction in major CV endpoints or mortality. The Look AHEAD (Action for Health in Diabetes) trial was the largest randomized trial to date evaluating the efficacy of a physical activity and dietary control intervention (targeting a ≥7% weight loss), in older adults with type 2 diabetes (22). In this study, at least 175 min/week of unsupervised exercise was targeted as part of the Intense Lifestyle Intervention (ILI), while the control group (Diabetes Support and Education-DSE group) received usual care. After a median follow up of 9.6 years, the composite primary outcome (death from CV causes, nonfatal MI, nonfatal stroke and hospitalization for angina) occurred in a similar number of participants in the intervention and control groups (22). Possible reasons for this finding include the lower-than-expected rates of CV events in both groups, improved overall CV risk factor treatment with antihypertensive agents and statins, enrollment of a relatively healthy population and gradual weight loss in the control group (difference in weight loss between the 2 groups was 2.5% at the end of the study). Importantly, and perhaps one explanation for why there was no significant effect on CVD outcomes, after the first year of the trial, the intervention group and the control group were virtually performing the same amounts of exercise and physical activity (see Physical Activity and Diabetes chapter, p. S54).

Several prospective cohort studies have shown that physical activity is associated with improvement in CV outcomes and a reduction in CV and overall mortality in people with type 2 diabetes or impaired glucose tolerance and CVD. In the Nurses' Health Study, among women who reported having type 2 diabetes, the women who spent at least 4 hours per week performing moderate (including walking) or vigorous exercise had a 40% lower risk of developing CVD (including coronary heart disease [CHD] and stroke) than those who did not. In another study of 2,896 adults with diabetes, those who walked for at least 2 hours per week had lower CV mortality rates compared to inactive individuals (hazard ratio [HR] 0.66, 95% CI 0.45–0.96) (23). Rates were even lower for those who walked 3 to 4 hours per week (HR 0.47, 95% CI 0.24–0.91).

Nutrition therapy

The CVD event risk reduction benefits of a Mediterranean style diet are well documented (see Nutrition Therapy chapter, p. S64) and may be related to anti-inflammatory and antioxidative effects. The PREDIMED (Prevencion con Dieta Mediterranea trial) randomized nearly 7,500 participants at high CV risk to a Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts, or to a control diet. About 50% of participants had type 2 diabetes. The trial was stopped early after a 30% reduction in the primary

composite outcome of CV death, MI or stroke was observed with the Mediterranean diet. People with existing diabetes (n=3,614) had results similar to the main trial population.

Weight management

No randomized prospective trials, including the Look AHEAD trial discussed above, have shown a reduction in major CV endpoints or mortality with weight loss in people with diabetes and obesity (22) (see Physical Activity and Diabetes chapter, p. S54).

Glycemic control

The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes (24), the Kumamoto trial (25), and the United Kingdom Prospective Diabetes Study (UKPDS) (26,27) in type 2 diabetes demonstrated that improved glycemic control significantly reduced the risk of microvascular complications, but had no significant effect on CV outcomes. Subsequent observational data from long-term follow up after termination of randomization periods of both the DCCT and UKPDS cohorts showed a persistence of significant microvascular benefits and also demonstrated an emergence of beneficial effect on CV outcomes attributed to intensive glycemic control (28,29) (see Targets for Glycemic Control chapter, p. S42).

Three major randomized controlled trials—the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (30), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (31,32), and Veterans Affairs Diabetes Trial (VADT) (33,34)—examined the effect of intensive glycemic control on middle-aged or older (mean age 60 to 68 years) participants with established type 2 diabetes for 8 to 11 years, with either CVD or multiple CVD risk factors. These studies compared intensive glycemic control with an A1C of 6.4% to 6.9% vs. 7.0% to 8.4% in the standard glycemic control cohort. No benefit on CV outcomes was seen in any of the 3 studies. The ACCORD trial was stopped early because of a 22% increase in all-cause mortality (HR 1.22, 95% CI 1.01-1.46) driven predominantly by CV mortality (30). The reasons for the increased mortality associated with intensive glycemic control are unclear (see Targets for Glycemic Control chapter, p. S42).

A retrospective analyses of data from the ADVANCE trial suggests that visit-to-visit variability in A1C and fasting plasma glucose predicted future CV events, microvascular events and all-cause mortality independent of CVD risk factors (35). Glycemic variability has been linked to mitochondrial superoxide overproduction, and oxidative stress is a key driver of atherosclerotic disease development and progression (36–39). In addition, glycemic variability has been linked to increases in inflammatory cytokines and increased macrophage and monocyte adhesion to the vascular endothelium, also promoting the development and progression of atherosclerosis (35–39). In one cohort study of >5,000 people with type 2 diabetes, time-dependent variation of fasting glycemia was a strong predictor of all-cause and CV mortality (40) (see Targets for Glycemic Control chapter, p. S42).

Antihyperglycemic agents

Based on controversies regarding rosiglitazone, in 2008, the United States Food and Drug Administration (FDA) required that all new antidiabetic therapies undergo evaluation for CV safety at the time of approval. Since then, several trials have reported evaluations of dipeptidyl peptidase (DPP)-4 inhibitors (41–43), glucagon-like polypeptide (GLP)-1 receptor agonists (44–46), sodium-glucose cotransporter (SGLT)-2 inhibitors (47,48) and insulin (49); and many other trials are underway. These studies were done in high-risk people with diabetes with either established CVD or multiple CV risk factors, and are discussed in detail in the Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88).

In general, the DPP-4 inhibitors studied thus far have demonstrated non-inferiority/safety for MACE. The exception was the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial with saxagliptin, where there was an observed increase in the risk of hospitalization for heart failure (41).

In the Empagliflozin Cardiovascular Outcome Event (EMPA-REG OUTCOME) trial, which included 7,020 people with type 2 diabetes and clinical CVD, the SGLT2 inhibitor, empagliflozin, demonstrated a significant reduction in MACE and heart failure hospitalizations, driven by a marked reduction in CV mortality and all-cause mortality (47). There was no heterogeneity observed between the doses of empagliflozin 10 mg or 25 mg, and therapy was generally very well tolerated. Although the exact mechanism(s) of benefit of empagliflozin remains unclear, the observed CVD risk reduction was driven by a reduction in hospitalization for heart failure and CV mortality and not via a reduction in fatal and non-fatal atherothrombotic events. In the Canagliflozin Cardiovascular Assessment (CANVAS) Study, which combined data from 2 trials involving a total of 10,142 participants with type 2 diabetes and high CV risk, the SGLT2 inhibitor, canagliflozin, demonstrated a reduction in MACE (48); however, there was an increase in the risk of lower limb amputations and fractures in the canagliflozin group.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial enrolled 9,340 participants with longstanding type 2 diabetes (45). The majority of participants (81%) were ≥50 years of age on pre-existing antihyperglycemic therapy with at least 1 CV condition (coronary heart disease, cerebrovascular disease, peripheral arterial disease, heart failure, or stage 3 or higher chronic kidney disease [CKD]). Over a median follow up of 3.8 years, fewer participants in the GLP-1 receptor agonist, liraglutide, arm compared to placebo had the primary endpoint of CV death, nonfatal MI or nonfatal stroke (13.0% vs. 14.9%, respectively; HR 0.87, 95% CI 0.78–0.97), fulfilling the statistical criteria for both noninferiority ($p<0.001$) and superiority ($p=0.01$). The Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) enrolled 3,297 participants with a mean duration of type 2 diabetes of 13.9 years (46). At baseline, 83% had established CVD or stage 3 or higher CKD. After a median follow up of 2.1 years, the primary composite outcome of CV death, nonfatal MI or nonfatal stroke occurred in 6.6% of participants treated with the GLP-1 receptor agonist, semaglutide, and 8.9% of participants treated with placebo (HR 0.74, 95% CI 0.58–0.95), fulfilling statistical criteria for noninferiority ($p<0.001$); a non-pre-specified test for superiority was also significant ($p=0.02$).

The CV safety of sulfonylureas and meglitinides is uncertain (50,51). In a meta-analysis of 115 trials (of at least 6 months duration) comparing sulfonylureas with an active comparator in people with type 2 diabetes, there was no difference in the incidence of MACE, although overall mortality (but not CV mortality) was increased (odds ratio [OR] 1.22, 95% CI 1.01–1.49) (52). In a subsequent meta-analysis of 47 trials (of at least 1-year duration) comparing second-generation sulfonylureas (gliclazide, glimepiride) with diet, placebo or an active comparator, sulfonylureas were not associated with an increased risk of overall mortality, CV mortality, MI or stroke (53). Trials comparing metformin and sulfonylurea have suggested higher rates of cardiac events with sulfonylureas than metformin (54–56); however, it is not known whether the increase in CV risk is due to CV toxicity from sulfonylureas or from the possibly protective effects of metformin.

Blood pressure control

Hypertension is very common in persons with diabetes. Recommended BP targets and pharmacological therapies are discussed in the Treatment of Hypertension chapter, p. S186.

Antiplatelet therapy

Primary prevention. Platelets play a pivotal role in the development of atherosclerosis and vascular thrombosis. As people with diabetes have increased in vitro platelet reactivity and aggregation, they might be expected to have enhanced benefit from platelet inhibition with agents, such as acetylsalicylic acid (ASA). However, in vitro tests of platelet aggregation suggest that people with diabetes have platelets that are more likely to be resistant to the inhibitory effect of ASA (57,58). Thus, despite the proven advantages of ASA therapy in people with established CVD, the evidence for benefits of ASA therapy for the primary prevention of CVD events in persons with diabetes is less robust (59). More recently, a subgroup analysis of the Japanese Prevention of Atherosclerosis (JPAD) trial of ASA in the primary prevention of CVD events in diabetes has suggested that persons with diabetes and an elevated C-reactive protein level may benefit from ASA (60).

Pooled estimates suggest that, for primary prevention of CVD events in people with diabetes, ASA results in no reduction of MI and stroke, but an important increase in gastrointestinal hemorrhage (61–64).

Despite a plethora of data, there remains uncertainty about the use of ASA in the primary prevention of CVD events in persons with diabetes, and its routine use in primary CVD event prevention is not recommended. However, some people with multiple CV risk factors and evidence of vascular inflammation, as reflected by C-reactive protein levels, may cross the risk-benefit threshold in which the potential benefits justify the potential increase in hemorrhagic events.

Existing evidence suggests that some people with diabetes may be resistant to the effects of ASA for a number of reasons. The Study Comparing Cardiovascular Effects of Ticagrelor vs. Placebo in Patients with Type 2 Diabetes Mellitus (THEMIS) is currently underway and is examining the role of the adenosine receptor antagonist, ticagrelor, in primary prevention of MACE in people with type 2 diabetes (65).

Secondary prevention. ASA has been shown to reduce CVD events in people with and without diabetes and established CVD (66). The clinical trial evidence, as reflected in the 2011 Canadian Cardiovascular Society Guidelines on the "Use of Antiplatelet Therapy in the Outpatient Setting", supports the use of ASA 75 mg to 162 mg daily for the secondary prevention of CVD events in those with diabetes (67).

Clopidogrel 75 mg may be used in people unable to tolerate ASA. The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial found that clopidogrel had a modest and marginally significant advantage over aspirin for the prevention of stroke, MI, and vascular disease in 19,185 participants with a recent stroke, MI or peripheral artery disease (annual event rate 5.3% vs. 5.8%) although the study population was not specific for people with diabetes (68).

In addition, there is evidence from the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial to indicate that people with diabetes and a prior MI may experience a reduction in MACE from dual antiplatelet therapy, with both ASA and ticagrelor, when this therapy is extended more than 1 year beyond the original acute coronary event (69); however, increased major bleeding was observed (HR 2.56, 95% CI 1.52–4.33, p=0.0004).

Renin angiotensin aldosterone system (RAAS) inhibition

The benefit of angiotensin-converting enzyme (ACE) inhibition for CV protection with ramipril 10 mg daily was demonstrated by the Heart Outcomes Prevention Evaluation (HOPE) trial in participants with and without diabetes (70). It was also shown in the Micro-HOPE subset analysis of participants with diabetes, which enrolled individuals with diabetes, aged ≥55 years, with 1 other CV risk factor (total cholesterol >5.2 mmol/L, HDL-C <0.9 mmol/L, hypertension, microalbuminuria or smoking) or established CVD (71). In participants with diabetes enrolled in the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study, the benefits from perindopril 8 mg daily were similar to those observed in the overall group; however, in this subgroup, the sample size was too small to show a statistically significant benefit (72). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) indicated similar CV protective effect from the angiotensin receptor blocker (ARB) telmisartan 80 mg daily as the ACE inhibitor ramipril 10 mg daily in a subset of participants with diabetes (73).

Whether the benefits of ACE inhibition result from a reduction in BP or from an unique CV benefit remains controversial. The benefits of ACE inhibition in both the HOPE and EUROPA trials were observed in individuals with or without a history of hypertension, and in those with higher and lower BP readings (70,74). In the HOPE study, after adjustment for the changes in systolic (2.4 mmHg) and diastolic (1.0 mmHg) BPs, ramipril still lowered the risk of the combined primary outcome by 25% (95% CI 12–36, p=0.0004) (71).

One meta-analysis demonstrated a significant reduction in all-cause mortality, CV mortality and major CV events with ACE inhibitors in people with diabetes (75). Twenty-three of 35 identified trials compared ACE inhibitors with placebo (n=11) or active drugs (n=12) (32,827 participants) and 13 compared ARBs with active drugs (n=3) or placebo (n=10) (23,867 participants); the vast majority of studies were performed in participants with hypertension. When compared with controls (placebo/active treatment), ACE inhibitors significantly reduced the risk of all-cause mortality by 13% (risk reduction [RR] 0.87, 95% CI 0.78–0.98), CV deaths by 17% (RR 0.83, 95% CI 0.70–0.99) and major CV events by 14% (RR 0.86, 95% CI 0.77–0.95). Treatment with ARBs did not significantly affect all-cause mortality (RR 0.94, 95% CI 0.82–1.08), CV death rate (RR 1.21, 95% CI 0.81–1.80) and major CV events (RR 0.94, 95% CI 0.85–1.01).

In contrast, a recent meta-analyses of 19 randomized controlled trials (25,414 participants) that compared the use of ACE inhibitors and ARBs to other antihypertensive agents in people with diabetes found no difference in CV outcomes (76). When compared with other antihypertensive agents, ACE inhibitors and ARBs were associated with a similar risk of death (RR 0.99, 95% CI 0.93–1.05), CV death (RR 1.02, 95% CI 0.83–1.24) and MI (RR 0.87, 95% CI 0.64–1.18). There was also no difference in the hard renal outcome of ESRD (RR 0.99, 95% CI 0.78–1.28). Although the authors acknowledged that while doubling of creatinine is a stringent and commonly used endpoint and even though there are trials that have shown benefit of renin angiotensin aldosterone system (RAAS) on this outcome, doubling of creatinine was not consistently reported in the trials reviewed and was not examined explicitly in their analysis.

There is emerging uncertainty as to whether the use of RAAS blockade in people with diabetes, but without a history of hypertension or CV risk factors, derive a CV event reduction benefit from being placed on RAAS inhibition. Given the significant differences in the clinical trial protocols, the specific patient populations, the durations of the interventions, the conflicting findings between renal outcomes and CV outcomes, and the durations of the trial follow ups, it is difficult to state emphatically whether or not RAAS inhibition, independent of the presence of hypertension, is a benefit in all people with diabetes. The Vascular Protection in People with Diabetes chapter in the *Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* recommended that all people with diabetes ≥55 years of age be started on an ACE inhibitor or ARB, at doses that have

demonstrated vascular protection, even in the absence of a CV risk factor or end organ damage (i.e. albuminuria, retinopathy, left ventricular hypertrophy) (77). This Grade D, Consensus recommendation has been eliminated from the 2018 guidelines as no studies have clearly demonstrated CV benefit for this specific lower-risk population. However, it is important to recognize that the overwhelming majority of people with diabetes have additional compelling indications to be on RAAS inhibitors by age 55 years, almost always require multiple medications to achieve BP targets and almost always have suboptimal BP control. Therefore, the clinical likelihood that people with diabetes will end up on some form of RAAS inhibition remains extremely high. While the recommendation to use RAAS therapy in all adults ≥55 years has been removed, we strongly encourage clinicians to regularly evaluate CV risk in all persons with diabetes to ensure people with diabetes who would benefit from RAAS inhibition are identified and treated appropriately.

Lipid-modifying therapies

There is clinical trial evidence of the benefits of statin therapy for primary prevention in people with diabetes at ages prior to achieving a high proximate 10-year CVD risk. The Heart Protection Study (HPS) enrolled 5,963 individuals from age 40 years with diabetes, of whom 49% had no evidence of CVD (78). CV events were reduced by 22% (95% CI 13–30) in the participants with diabetes receiving simvastatin 40 mg daily for the 5-year treatment period (79). The same relative benefit was observed in participants with or without evidence of CVD. In the 615 participants with type 1 diabetes, there was a similar (although not statistically significant) risk reduction as observed in the 5,438 participants with type 2 diabetes. The Collaborative Atorvastatin Diabetes Study (CARDS) included 2,838 participants with diabetes, 1 CV risk factor and age >40 years (80). They were treated for an average of 3.9 years with either atorvastatin 10 mg daily or placebo. CV events were reduced by 37% (95% CI –52% to -17%, p=0.001) by atorvastatin compared to placebo, with a 36% reduction of acute coronary heart disease, a 31% reduction of coronary revascularization and a 48% reduction of stroke. There was a strong trend toward a 27% reduction in all-cause mortality (95% CI –48% to 1%, p=0.059). Consequently, both the HPS and CARDS studies provided evidence supporting the use of statin therapy for all people with diabetes ≥40 years of age with or without 1 CV risk factor. The CARDS study concluded with the statement: “The debate about whether all patients with type 2 diabetes warrant statin treatment should now focus on whether any patients can reliably be identified as being at sufficiently low risk for this safe and efficacious treatment to be withheld” (80).

As a direct reflection of the impact of diabetes on lifetime risk for CVD, increased vascular aging, premature development of CVD, shorter life expectancy for the individual with diabetes, poor predictive value of current risk models and studies demonstrating benefit of lipid lowering in people with diabetes, the current guidelines recommend statin therapy for primary CVD prevention for all people with diabetes ≥40 years of age. The guidelines also continue to support the use of statins in secondary prevention in those with evidence of end organ damage (CVD, microvascular disease, particularly albuminuria). In addition, there are other circumstances, not specific to diabetes, that may warrant statin therapy for a particular individual based on the *2016 Canadian Cardiovascular Society (CCS) Guidelines for the Management of Dyslipidemia* (81).

LDL-C reduction should aim to achieve targets recommended in the current guidelines, and statins should be prescribed up to the maximally tolerated and approved dose. However, the use of other lipid-lowering agents in addition to statins may be necessary in some patients to achieve LDL-C goals (see Dyslipidemia chapter, p. S178). The IMProved Reduction of Outcomes: Vytorin Efficacy International trial (IMPROVE-IT) showed that the addition of ezetimibe to simvastatin in participants with recent acute coronary syndrome imparted an incremental CVD event benefit compared to use of simvastatin alone and the magnitude of the event reduction was commensurate with the degree of additional LDL-C lowering imparted by ezetimibe. The mean LDL-C in the simvastatin plus ezetimibe arm was 1.4 mmol/L and 1.8 mmol/L in the simvastatin-treated cohort. The event reductions were particularly evident in people with type 2 diabetes (82). Whether this is a specific effect of this drug combination or simply a reflection of the additional reduction in LDL-C remains unknown; however, existing data point strongly to the additional reduction in LDL-C as being significantly beneficial in people with diabetes.

Most recently, proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have been shown to add clinically significant LDL-C lowering when added to standard therapy (83,84). The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study of evolocumab vs. placebo in stable CAD and CVD participants receiving moderate to high-dose statin therapy, demonstrated a 15% reduction in MACE (CV death, MI, stroke, hospital admission for unstable angina or coronary revascularization) (85). The study included more than 11,000 participants with diabetes and a sub-analysis revealed that risk reductions in participants with or without diabetes were similar (HR 0.83, 95% CI 0.75–0.93, p=0·0008 for participants with diabetes and 0.87, 95% Cl 0·79–0·96, p=0·0052 for participants without diabetes) (86).

RECOMMENDATIONS

1. All individuals with diabetes should follow a comprehensive, multifaceted approach to reduce CV risk, including:
   a. A1C ≤7.0% implemented early in the course of diabetes [Grade C, Level 3 (28,29)]
   b. Systolic BP of <130 mmHg [Grade C, Level 3 (87)] and diastolic BP of <80 mmHg [Grade B, Level 1 (88)] (see Treatment of Hypertension chapter, p. S186)
   c. Additional vascular-protective medications in the majority of adults with diabetes (see recommendations below) [Grade A, Level 1 (3,4) for those with type 2 diabetes age >40 years with albuminuria; Grade D, Consensus for those with type 1 diabetes]
   d. Achievement and maintenance of healthy weight goals [Grade D, Consensus]
   e. Healthy eating (see Nutrition Therapy chapter, p. S64 for specific dietary recommendations)
   f. Regular physical activity [Grade D, Consensus] (see Physical Activity chapter, p. S54)
   g. Smoking cessation [Grade C, Level 3 (20)].

2. Statin therapy should be used to reduce CV risk in adults with type 1 or type 2 diabetes with any of the following features:
   a. Clinical CVD [Grade A, Level 1 (79)]
   b. Age ≥40 years [Grade A, Level 1 (79,80), for type 2 diabetes; Grade D, Consensus for type 1 diabetes]
   c. Age <40 years and 1 of the following:
      i. Diabetes duration >15 years and age >30 years [Grade D, Consensus]
      ii. Microvascular complications [Grade D, Consensus]
      iii. Warrants therapy based on the presence of other CV risk factors according to the *2016 Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia* (81) [Grade D, Consensus].

3. For individuals not at LDL-C goal despite statin therapy, a combination of statin therapy with second-line agents may be used to achieve the goal and the agent used should be selected based upon the size of the existing gap to LDL-C goal [Grade D, Consensus]. Generally, ezetimibe should be considered [Grade D, Consensus]. In people with diabetes who also have concomitant clinical CVD, ezetimibe or evolocumab may be used to further reduce major adverse cardiac events [Grade A, Level 1 (82) for ezetimibe, Grade A, Level 1 (85) for evolocumab], and they should also be considered in those with concomitant familial hypercholesterolemia [Grade D, Consensus for ezetimibe and PCSK9 inhibitor].

4. ACE inhibitor or ARB, at doses that have demonstrated vascular protection, should be used to reduce CV risk in adults with type 1 or type 2 diabetes with any of the following:
   a. Clinical CVD [Grade A, Level 1 (70,73)]
   b. Age ≥55 years with an additional CV risk factor or end organ damage (albuminuria, retinopathy, left ventricular hypertrophy) [Grade A, Level 1 (70,73)]
   c. Microvascular complications [Grade D, Consensus].

Note: Among women with childbearing potential, ACE inhibitors, ARBs or statins should only be used if there is reliable contraception.

5. In people with established CVD, low-dose ASA therapy (81–162 mg) should be used to prevent CV events [Grade B, Level 2 (66)].

6. ASA should not be used routinely for the primary prevention of CVD events in people with diabetes [Grade A, Level 1A (62–64)]. ASA may be used in the presence of additional CV risk factors [Grade D, Consensus].

7. Clopidogrel 75 mg may be used in people unable to tolerate ASA [Grade D, Consensus].

8. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR > 30mL/min/1.73 m^2, an antihyperglycemic agent with demonstrated CV outcome benefit should be added to reduce the risk of major CV events [Grade A, Level 1A (47) for empagliflozin; Grade A, Level 1A for liraglutide (45); Grade C, Level 2 for canagliflozin (48) (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88).

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *BP*, blood pressure; *CAD*, coronary artery disease; *CI*, confidence interval; *CKD*, chronic kidney disease; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CKD*, chronic kidney disease; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *MACE*, major cardiovascular events; *NNT*, number needed to treat; *RAAS*, renin angiotensin aldosterone system; *RR*, relative risk.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Physical Activity and Diabetes, p. S54
Nutrition Therapy, p. S64
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Weight Management in Diabetes, p. S124
Dyslipidemia, p. S178
Treatment of Hypertension, p. S186

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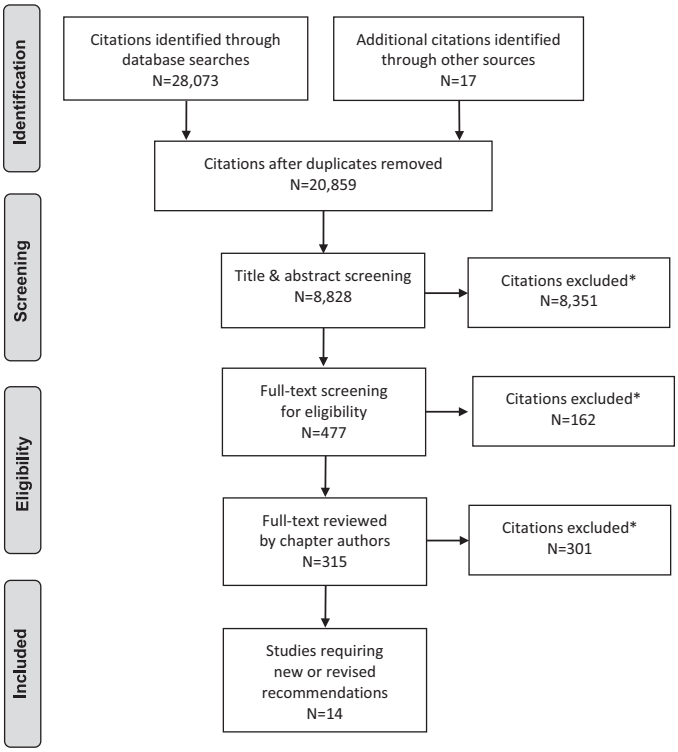
Literature Review Flow Diagram for Chapter 23: Cardiovascular Protection in People with Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (89).

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2018 Clinical Practice Guidelines

Screening for the Presence of Cardiovascular Disease

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Compared to people without diabetes, individuals with type 1 and type 2 diabetes (especially women) are at higher risk of developing heart disease, and at an earlier age. Unfortunately, a large proportion will have no symptoms before either a fatal or a nonfatal myocardial infarction (MI). Hence, it is desirable to identify people at high risk for cardiovascular events, especially people with unknown established severe coronary artery disease.
- In individuals at high risk of coronary artery disease (based on age, gender, description of chest pain, history of prior MI, abnormal resting electrocardiogram and presence of several other cardiovascular risk factors), exercise stress testing is useful for the assessment of prognosis.
- Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and unknown vascular disease. For those unable to perform an exercise test, imaging testing, such as pharmacologic, nuclear stress imaging, stress echocardiography, coronary artery calcium scoring or coronary computed tomography angiography may be required. Most imaging techniques have been shown to be useful in prospective study in order to identify people at higher risk. However, so far, there is no head-to-head study showing which one is most cost-effective.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- People with diabetes are at increased risk for developing heart disease, and often present at an earlier age than people without diabetes.
- Discuss with your health-care provider how to screen for heart disease.

Introduction

The majority (65% to 80%) of people with diabetes will die from heart disease (1,2). Compared to people without diabetes, people with diabetes (especially women) are at higher risk of developing atherosclerotic disease, and at an earlier age. A high proportion of deaths occur in people with diabetes with no prior signs or symptoms of cardiovascular disease (CVD). Furthermore, people with diabetes have a high prevalence of silent myocardial ischemia, and almost one-third of myocardial infarctions (MIs) occur without recognized or typical symptoms (silent MIs) (3). The goals of screening are to improve life expectancy and quality of life by preventing MI and heart failure through the early detection of significant CVD.

The concept of coronary risk equivalency in people with type 2 diabetes has been challenged and a meta-analysis reported that this is not the case (4). Therefore, there is heterogeneity in the CVD risk of people with diabetes, which needs to be better defined clinically. For any degree of perfusion abnormality, people with diabetes had a much greater risk of cardiac events and death compared with people without diabetes (5). Similar findings have been reported for stress echocardiographic techniques (6) and electron-beam computed tomography studies (7).

In general, good clinical practice considers screening for any disease appropriate only when an effective treatment is available. Hence the underlying assumption of a study wishing to evaluate if screening for CVD is worthwhile in terms of survival, is that an effective treatment is available and the study design should reflect this by testing screening and treatment together. This is not the case looking at the literature of screening for coronary artery disease (CAD) in people with diabetes (8,9). On the other hand, The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (10) and the subsequent Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (11) represent the landmark trials in the field of stable CAD treatment. Both studies found no benefits in terms of survival of revascularization (surgical or percutaneous) over medical therapy in stable people with documented coronary artery stenosis. Of note, participants with markedly positive stress test were excluded in COURAGE. The Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients? (DADDY) study main finding reported that screening for CAD and revascularization did not affect the occurrence of a first cardiac event in people with diabetes (12). These results are in line with the Detection of Ischemia in Asymptomatic Diabetes (DIAD), COURAGE and BARI 2D studies and confirm that to date there is no proven indication, in daily practice, to search for ischemia in people with diabetes without symptoms. However, when one is clinically suspicious of the presence of CVD, different modalities can be used to assess the presence of CAD in people with diabetes.

Role of stress testing

Exercise stress testing is useful in people with diabetes at high risk of CAD for the assessment of prognosis and the identification of individuals who may benefit from coronary artery revascularization to improve long-term survival. The most predictive clinical observation for CAD in the person with or without

Conflict of interest statements can be found on page S175.

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diabetes is a history of chest pain or discomfort, but these features will be absent in a significant proportion (20% to 50%) of individuals with diabetes (13–19). Clinical findings, such as dyspnea on exertion, resting electrocardiogram (ECG) abnormalities or multiple CVD risk factors for atherosclerosis, may also indicate the presence of CAD. Recognition of such features is of clinical importance, as the outcome of CAD events is worse in people with diabetes when shortness of breath is the primary symptom (13).

The presence of CAD risk factors and resting ECG abnormalities identify people with diabetes at increased risk of important CAD burden and abnormal stress ECG or perfusion imaging results (20). A resting ECG at the time of diagnosis of diabetes also provides a baseline to which future ECGs can be compared. In people with diabetes considered to be at high risk for CAD, a repeat resting ECG may detect changes that result from silent MI and lead to earlier detection of critical CAD. There is evidence that early screening and intervention in people with diabetes and silent ischemia is beneficial and may improve long-term survival (16,21). Screening with exercise ECG stress testing will find 3-vessel CAD in 13% to 15% of those with abnormal stress test findings (22) and lead to angiography with revascularization in 1% to 3% of asymptomatic individuals (22–24). Similar findings were reported recently in The For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64: A Randomized Control Study (FACTOR-64) trial. It randomized 900 participants to coronary computerized tomography angiography (CTA) screening (n=452) or standard care (n=448). CTA showed no CAD in 31%, mild stenosis in 46%, moderate in 12% and severe stenosis in 11% of the participants. Although there was no significant reduction in CHD events in this 900-person study, the authors concluded that coronary CTA screening led to more aggressive risk factor modification in 70% of participants, including improvements in statin use and more serum lipids and systemic BP (25).

The Definition of Ischemia in Asymptomatic Diabetes (DIAD) study prospectively investigated the value of routine adenosine stress myocardial perfusion scanning in asymptomatic people with type 2 diabetes ≥55 years for the prevention of coronary events (19). The baseline study showed either perfusion defects or stress-induced ECG abnormalities in 22% of participants and large defects in 6%. In this study, multiple risk factors for CAD did not help identify people with positive functional tests for CAD. Of note, baseline ECG was normal in all participants. A substantial portion of the DIAD population was defined as having intermediate/high baseline CV risk. Nevertheless, their annual CV event rate was low and not altered by routine screening for inducible ischemia. Yet, a randomized pilot study on the impact of stress testing to screen for CAD in asymptomatic subjects with diabetes suggested a significant reduction in cardiac death and MI (26). Larger and adequately powered studies are necessary to support this provocative observation before clinical practice is changed. In the Basel Asymptomatic high-Risk Diabetics' Outcome Trial, almost one-quarter of the 400 asymptomatic participants with type 2 diabetes had silent myocardial ischemia, which was associated with a worse outcome (27). The yield of myocardial perfusion imaging can be improved by selecting a higher-risk group of people with diabetes with symptoms, peripheral vascular disease (PVD), chronic kidney disease (CKD), an abnormal ECG or a high coronary artery calcium (CAC) score (e.g. >400 Agatston score) (28). The choice of initial stress test should be based on evaluation of the resting ECG, the individual's ability to exercise, and local expertise and technology. Thus, the yield of stress testing in asymptomatic people with diabetes can be improved by selecting people based on the pre-test probability of CAD. The retrospective studies that showed a high prevalence of stress test abnormalities included people with abnormal ECGs (43% with Q waves) and vascular disease (28%) (28).

Data using diverse imaging technology have been reviewed and reported recently (28), but the additional benefit of imaging on prognosis and quality of life is not clear. Studies using coronary CTA in asymptomatic people with diabetes mostly concluded that these people have a high prevalence of coronary atherosclerosis and obstructive CAD, as well as a higher prevalence of plaques with features of instability compared with subjects without diabetes. Furthermore, it is important to emphasize that a normal ECG does not offer a long-term warranty from CVD events in people with type 2 diabetes. It is the same with stress echocardiography and myocardial perfusion imaging where no events were recorded in the first 2 years of follow up among people with a normal stress echocardiography or normal nuclear scan but significantly increased thereafter (6,28–30).

People with diabetes without evidence of CAD seen on computed tomography coronary angiography have an excellent prognosis, with no cardiac events at 62-month follow up. Thus, this imaging modality can be a useful tool to reassure people with diabetes with suspected CAD regarding their outcome, with a warranty period of at least 5 years in the presence of a normal result (5,31). Of note, coronary CTA is often performed in addition to a standard diagnostic work-up. This approach may be particularly useful in specific subsets of people with diabetes with unknown CAD and equivocal or uninterpretable stress tests or in case of a discrepancy between clinical presentation and stress test results. Owing to the high prevalence of CAD, the role of coronary imaging in people with diabetes may be not to document the presence of coronary atherosclerosis but rather to identify those people with more extensive disease vs. those without any atherosclerosis. Although CT coronary angiography is able to predict the prognosis of people with diabetes on the basis of the presence/extent of CAD and plaque type, coronary imaging by computed tomography coronary angiography is not, as in case of invasive angiography, able to predict which plaque may progress to destabilization and rupture, potentially causing a clinical event.

ECG abnormalities that limit the diagnostic accuracy of a stress ECG include resting ST depression (1 mm), left bundle branch block or right bundle branch block, an intraventricular conduction defect with QRS duration >120 ms, ventricular paced rhythm or pre-excitation. Individuals with these resting ECG findings should have a stress test with an imaging modality, such as scintigraphic myocardial perfusion imaging or echocardiography. The role of other imaging modalities (anatomical imaging), such as coronary CT, calcium score, etc., in comparison to functional imaging, needs to be determined in individuals with diabetes.

Exercise stress testing can identify people with diabetes with silent ischemia; however, whether at large exercise testing results in improved outcomes in people with diabetes has not been demonstrated. The strongest and most consistent prognostic marker identified during exercise ECG stress testing is the person's maximum exercise capacity (13). Although exercise capacity is decreased in individuals with diabetes (32–34), it is still of prognostic importance (13). Silent ischemia is most likely to occur in individuals with diabetes who are older (mean age 65 years) and have elevated total cholesterol and proteinuria (23).

An ECG with ST-T abnormalities at rest has been shown to be most predictive for silent ischemia (Odds Ratio 9.27, 95% CI 4.44–19.38) and was the only significant predictor of silent ischemia in women (23). The relevance of ST-T abnormalities as a predictive factor for silent ischemia emphasizes the importance of recording a resting ECG in most individuals with type 2 diabetes. An abnormal ECG may indicate the need for further investigations and result in the earlier detection and more aggressive management of CAD (23). An abnormal exercise ECG is associated with an annual CAD event rate of 2.1%, compared with 0.97% in subjects with normal exercise ECG (26).

Myocardial ischemia (whether silent or symptomatic) detected during exercise stress testing in individuals with diabetes is associated with poorer long-term survival compared to individuals without diabetes (16). Silent MI is common (40%) in older asymptomatic individuals with type 2 diabetes, but is more frequent (65%) in those with diabetes who also have microalbuminuria (35). People with diabetes and silent ischemia have an annual event rate for CAD of 6.2% (50% of events were new-onset angina and 50% were cardiac death or MIs) (36). Thus, silent MI is a prelude not only to symptomatic ischemia, but also to potentially fatal events. Also, it has been shown in a randomized trial in people with silent ischemia (the vast majority of whom did not have diabetes) that long-term anti-ischemic drug therapy (11 years follow up) reduces cardiac events (cardiac death, nonfatal MI, acute coronary syndrome or revascularization) with preservation of ejection fraction (37). In a retrospective study analyzing 14,849 consecutive people (3,654 with diabetes and 11,195 without diabetes) undergoing a combination of exercise stress and pharmacologic stress testing (combined protocol received intravenous dipyridamole [0.56 mg/kg] infusion over 4 minutes followed shortly by symptom-limited treadmill exercise), it was observed that, despite significant perfusion defects, people with diabetes who achieve ≥5 metabolic equivalents (METs) during exercise stress single-photon emission-computed tomography (SPECT) myocardial perfusion imaging (MPI) have significantly reduced risk for future cardiac events. People with diabetes who achieved a high workload (≥10 METS) had a low annualized event rate of 0.9% (38). The importance of low exercise capacity associated to worse CVD outcomes has been also observed in a smaller study (39).

Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and unknown vascular disease in this population. Individuals who cannot adequately exercise on a stress test have a poorer prognosis than those who can, regardless of the reason for this incapacity. Perfusion imaging also provides important prognostic information. Myocardial perfusion imaging has similar predictive value for cardiac death and nonfatal MI in individuals with diabetes as in those without diabetes (40). For those unable to perform an exercise ECG stress test, pharmacologic stress imaging, using dipyridamole, adenosine or dobutamine testing, is required. Stress echocardiography and stress nuclear imaging have similar values for cardiac events in the general population (41), but no comparative data are available for the person with diabetes. In a meta-analysis of perfusion imaging, an abnormal scan was predictive of future CAD events in subjects with and without diabetes. However, the cardiac event rate in individuals with diabetes was significantly greater than in those without diabetes (41). The choice of the optimal imaging modality to detect stress-induced MI is best determined by local availability and expertise.

The utility of newer CAD diagnostic modalities, such as coronary CTA, CAC scoring and cardiac magnetic resonance imaging, is currently unknown in terms of guiding management decisions in patients with type 2 diabetes (42). Coronary CTA has emerged as a noninvasive tool for the diagnosis of CAD that enables assessment of the vascular lumen together with the arterial wall. Multidetector coronary CTA allows assessment of coronary atherosclerosis at an earlier stage compared with imaging techniques that help evaluate myocardial perfusion. The long-term prognostic value of coronary CTA in a large population of people with diabetes without chest pain syndrome was investigated (43). Coronary CTA demonstrated a high prevalence of CAD (85%), mostly non-obstructive CAD (51%). People with events were more often classified in a higher CAC-risk category but coronary CTA performed better than the CAC-score regarding the events prediction (43).

Studies have demonstrated that increased CAC in persons with diabetes is associated with increased prevalence of ischemic events and mortality and is a better predictor than the Framingham risk score (28). Also, it was reported in 392 people with type 2 diabetes that the best predictors of progression were baseline CAC score, statin use and A1C >7.0% during follow up (44). Of importance, people with diabetes but with no CAC demonstrated a survival rate similar to that of people without diabetes and no detectable calcium (5,7).

Peripheral Vascular Disease

Palpation of peripheral pulses is a routine clinical examination recommended in people with type 2 diabetes, especially those with suspected peripheral arterial disease (PAD). The procedure is simple, rapid, noninvasive and inexpensive, but it has high interobserver variability, depending on foot anatomic variation, clinician experience and patient examination conditions (45,46). The examination of peripheral pulses also is hampered by the presence of medial arterial calcification, which is common in people with diabetes (47).

PAD is a common manifestation of atherosclerosis in type 2 diabetes. PAD is especially frequent in people with type 2 diabetes, with an approximately threefold increased risk compared with a population without diabetes (48). PAD mainly affects the infrapopliteal arteries and may induce more damage in small than in large vessels in people with type 2 diabetes (49,50). In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) clinical trial, the incidence of PAD was comparable to the incidence of major coronary events and stroke and intensive glucose intervention did not influence the risk for major PAD in participants free from PAD at baseline (HR 0.96, 95% CI 0.82–1.12, p=0.62) (51). The risk for PAD was also similar in participants randomly assigned to active BP treatment compared with placebo (HR 1.08, p=0.36) and in those assigned to both intensive glucose control and active BP treatment compared with standard glycemic control and placebo (HR 1.03, p=0.77) (51).

The impact of previous microvascular and CV disease on the risk of major PAD was analyzed in 10,624 people with type 2 diabetes free from baseline major PAD in the ADVANCE trial. Microvascular disease, particularly macroalbuminuria and retinal photocoagulation therapy, strongly predicts major PAD in people with type 2 diabetes, but CVD does not (52). In ADVANCE, higher A1C and urinary albumin to creatinine ratio (ACR) levels, absence of dorsalis pedis and posterior tibial pulses, and current smoking history at baseline, higher systolic and lower diastolic BP, both with use of antihypertensive drugs, were all independently associated with the risk for major PAD (52). In the UK Prospective Diabetes Study (UKPDS), age, A1C, systolic BP, high density lipoprotein cholesterol (HDL-C), previous CV disease and current smoking were found to be independent risk factors for PAD (53). In the BARI 2D trial, age, female sex, black African origin, smoking, pulse pressure, A1C and ACR were independent risk factors for PAD (54,55). The incidence rate of PAD was 3.5 times higher in BARI 2D than in ADVANCE, which may be explained by differences in each study's inclusion criteria and the definitions of PAD outcomes.

From an ethnic viewpoint, there may be a lower prevalence of PAD in people with diabetes and CVD from South Asia compared with those of white European descent (52,56). Absent dorsalis pedis and/or posterior tibial pulses are independent predictors of major vascular outcomes in people with type 2 diabetes (57). Indeed, absent compared with present peripheral pulses (n=2218) were associated with increased 5-year risks for major CV events (HR 1.47, p<0.0001), MI (HR 1.45, p=0.003), stroke (HR 1.57, p=0.0003), CV death (HR 1.61, p<0.0001), heart failure (HR 1.49, p=0.0002), all-cause mortality (HR 1.48, p<0.0001), major microvascular events (HR 1.17, p=0.04), nephropathy (HR 1.24, p=0.04), ESRD or renal death (HR 2.04, p=0.02) and peripheral neuropathy (HR 1.13, p=0.0008)

after multiple adjustment (57). Compared with the presence of all peripheral pulses, the absence of at least 1 peripheral pulse was significantly associated with a higher incidence of major CV events, nonfatal MI, nonfatal stroke, CV death, heart failure, all-cause mortality, major microvascular events, new or worsening nephropathy, ESRD or renal death, new or worsening peripheral neuropathy and all-cause hospitalization.

It is important to emphasize that compared with the ankle-brachial index or other noninvasive vascular methods, the pedal pulse examination has a weak performance for the diagnosis of PAD (58–60), especially the dorsalis pedis pulse, which may be absent in healthy subjects without PAD (61). A previous study estimated the sensitivity and specificity of an abnormal dorsalis pedis pulse for the detection of PAD at 50% and 73%, respectively, and at 71% and 91%, respectively, for an abnormal posterior tibial pulse (58). Other studies reported that the sensitivity and specificity of undetectable pedal pulses varied from 5% to 32% and 98% to 99%, respectively (59,60). Nevertheless, the absence of peripheral pulses has been shown to be a strong and independent predictor of risk for major outcomes, especially major CV events, CV and all-cause mortality, heart failure and renal events, in people with type 2 diabetes (57). This data should encourage the examination of peripheral pulses to improve the early detection and treatment of vascular complications in people with type 2 diabetes, especially in areas with limited access to specialized medical centres and technical resources. Therefore, these simple clinical indicators should be used to improve risk stratification and treatment of these people.

CVD in Type 1 Diabetes

Incidence and prevalence of CVD

CVD complications are important causes of morbidity and mortality among individuals with type 1 diabetes, which may have been under-recognized in the past. The presence of late gadolinium hyper-enhancement is a marker of prior MI in people with diabetes with unsuspected CAD. Late gadolinium hyper-enhancement was demonstrated in 4.3% of asymptomatic people with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial (62). Reported prevalence rates of CVD in type 1 diabetes vary between 3% and 12.4% (63–65). It is important to emphasize that the CVD risk burden and profile of people with type 1 diabetes differs from type 2 diabetes. The Diabetes United Kingdom longitudinal cohort study, including more than 7,000 participants with type 1 diabetes, reported that type 1 diabetes is associated with markedly increased adjusted HR for major CAD events (median follow up of 4.7 years) in both men (HR 3.6) and women (HR 9.6). Of such, these risk increments are comparable to those observed in people with type 2 diabetes (65). Major CVD events occurred in type 1 diabetes on average 10 to 15 years earlier compared with matched controls without diabetes. The age-adjusted relative risk for CVD in type 1 diabetes is 10 times that of the general population (66–68). The Pittsburgh Epidemiology of Diabetes Complications (EDC) study demonstrated that the incidence of major CVD events in young adults with type 1 diabetes (age 28 to 38 years) was 0.98% per year (69) and was as high as 3% per year after age 55 years, making it the leading cause of death in that population (64,65,70). Gender and race/ethnicity are important features of increased risk of CVD; male gender and African Americans have higher rates of CVD compared to Europeans (69).

Difference from type 2 diabetes

CVD in type 1 diabetes differs from type 2 diabetes, not only in that it presents at a younger age, but also in relation to gender, silent presentation and disease severity (66,67). There is a high prevalence of silent CAD in young adults with type 1 diabetes, which may be related to cardiac autonomic neuropathy. Finally, the disease process seems to be more severe in type 1 diabetes. Compared with controls without diabetes, people with type 1 diabetes are more likely to have severe coronary stenoses, involvement of all 3 major coronary arteries and distal segment disease, resulting in major CV events with poor outcome and/or early development of heart failure (66,67).

CAD and cerebrovascular disease

CAD appears to be more common than stroke. The cumulative incidence of CAD ranges between 2.1% (64) and 19% (71) depending on the characteristics of the population studied. For the most part, studies report an incidence of around 15% (65,72,73). Mortality rates from CAD are reported between 6% and 8% (71,73), are likely higher in men than women (in contrast to type 2 diabetes) (74), and in those >40 years of age compared to those <40 years of age (74). Stroke is still an important outcome in type 1 diabetes; the cumulative incidence of stroke was 3.3% over 6 years among African Americans (66), 5.9% over 20 years in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (72), and 0.74% per year in the EURODIAB study (64). Also, prevalence of silent brain infarcts or leukoaraiosis is extremely high (34.5%) in type 1 diabetes (75).

Peripheral vascular disease

PVD is an important vascular complication of type 1 diabetes. Incidence rates of lower extremity amputation vary by age from 3.6 per 1,000 person-years among individuals 25 to 44 years of age to as high as 7.2% (76). By age 65, the cumulative probability of PVD is 11% in women and 20.7% in men (77). Compared to the general population, the rate of PVD among those with type 1 diabetes may be very high (77). If one considers ankle-brachial index (ABI) <0.9 as the criterion for the presence of peripheral atherosclerotic disease instead of overt clinical events, 45.6% of participants from DCCT/EDIC study developed PVD (78). Predictors of PVD include increasing age, male gender, history of sores or ulcers, diastolic blood pressure, LDL-C, A1C, diabetes duration, hypertension, albumin excretion rate, glomerular filtration rate, smoking and retinopathy (76,78,79). In addition to the clinical endpoints of CAD, stroke and PVD, subclinical carotid disease may be commonly associated with type 1 diabetes. Compared to age-/sex-matched healthy controls, greater carotid intima-media thickness (IMT) has been observed in studies of children with type 1 diabetes with a mean age as young as 11 years (80–83).

Time course of events

Although CAD rarely presents within the first 20 years of diagnosis, by age 30 years, many individuals will have had type 1 diabetes for 20 years and rates of CVD begin to approach the high-risk category (84). The recent decline in CKD in diabetes has not been accompanied by a corresponding fall in CAD rates. Indeed, no temporal decline was noted for the cumulative incidence of MI/CAD death at 20, 25, or 30 years' duration of diabetes in the Pittsburgh EDC, despite at least a 50% decrement of the cumulative incidence of overt nephropathy (69). In fact, nephropathy or microalbuminuria no longer precedes CAD in the majority of cases. In the EDC study, there was no difference in the cumulative incidence of CAD stratified according to year of diagnosis (1950–1980), despite substantial declines in renal failure, as well as decline in overall mortality over the same time period (69). The DCCT intensive therapy intervention had a significant impact on the age and

the duration of diabetes exposure at onset of CVD, despite the fact that no overt CVD was apparent at baseline (85). Thus, despite the well-recognized increase in CVD risk associated with proteinuria, it clearly explains only a portion of the CVD risk. In the DCCT study, the treatment group effect of intensive treatment therapy on CVD risk persisted after adjustment for microalbuminuria (HR 0.62) and albuminuria (HR 0.58), suggesting that, although diabetic kidney disease is important, differences in mean A1C are clearly significant drivers (85). In the same way, only 15% of the Oslo Study population had microalbuminuria, despite the fact that all participants had at least subclinical CAD (86). In the Pittsburgh EDC study, myocardial ischemia by ECG, as the initial manifestation of CAD, was less common and a documented MI was more common in those with prior renal disease compared to those without (87).

Effect of sex

Compared to women without diabetes, women with type 1 diabetes had a 3.5 times higher risk of having coronary artery calcification (88). While standardized mortality rates from ischemic heart disease were higher in men than women at all ages in the general population, there was no difference in mortality from ischemic heart disease in men and women with type 1 diabetes <40 years of age (74). Men with type 1 diabetes ≥40 years had a higher mortality rate from CVD than women with type 1 diabetes (89) in contrast to type 2 diabetes. In a large Norwegian cohort study, mortality rates from ischemic heart disease were higher in women with type 1 diabetes than in men or women without diabetes. However, men with type 1 diabetes had higher mortality rates than women with type 1 diabetes (90). A population-based cohort study showed different results (91). This study found that among those with type 1 diabetes, women had a 2.5 to 3 times higher standardized mortality rate from CVD than men with type 1 diabetes. Although not all the findings are consistent, the common thread in all these studies is that the presence of type 1 diabetes (as well as in type 2 diabetes) seems to dramatically increase the risk for CVD, particularly in women.

Testing for CVD in type 1 diabetes

In the absence of data to the contrary, one approach to identifying CVD in people with type 1 diabetes is to apply the same CAD risk assessment and diagnostic strategies used in type 2 diabetes (see discussion above) or in the population in general (92). This, however, does not support routine CAD screening beyond resting ECGs in people with diabetes who do not have CV symptoms or an abnormal ECG, favouring instead global CVD risk factor assessment and management.

People with type 1 diabetes who have symptoms suggestive of CAD, an abnormal resting ECG or clustering of CVD risk factors yielding an intermediate or high global risk estimate, acknowledging that risk scores are more or less accurate in type 1 diabetes, should have additional testing for CAD (92,93). For people able to walk on a treadmill without significant baseline ST segment abnormality (see discussion for type 2 diabetes), exercise treadmill testing remains the first-line diagnostic test due to the high cost efficacy and widespread availability. However, treadmill testing may not be possible due to the burden of peripheral neuropathy, foot pathology, lower extremity amputation and ECG abnormalities as left ventricular hypertrophy in the patient population with type 1 diabetes. Pharmacological stress imaging studies, such as nuclear myocardial perfusion imaging or pharmacological stress echocardiography may be required. Sophisticated testing has been reported in people with type 1 diabetes. CAC, assessed by CT imaging, is common (94,95) and more frequent in people with type 1 diabetes than in those without. In the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study, 656 adult participants with type 1 diabetes showed a higher prevalence and extent of CAC than 764 age- and sex-matched control subjects with no difference between sexes (96). Progression of CAC is reduced by intensive glycemic control (95). The presence of CAC is independently associated with increased prevalence of CAD, even after adjustment for traditional risk factors (94), and test performance in people with type 1 diabetes is comparable to that of the general population.

In the Pittsburgh EDC longitudinal study, 302 adults with type 1 diabetes, with a mean age of 38 years, underwent CAC screening. The prevalence of CAC was 11% in participants <30 years of age and as high as 88% among those 50 to 55 years. CAC was independently associated with prevalent CAD across the entire cohort, with a stronger graded association in men than in women. While CAC assessment has proven to predict subsequent CV risk in the general population and in cohorts of people with type 2 diabetes (7), no data are yet available to determine the utility of CAC assessment for risk prediction in type 1 diabetes. Women with type 1 diabetes had just as much CAC as men; women without diabetes have less CAC than men (88).

In summary, asymptomatic people with diabetes are considered to be in a high global CAD risk, for which exercise ECG is rated appropriate and cardiac imaging techniques (stress radionuclide imaging, stress echocardiography, stress cardiac magnetic resonance, calcium scoring and coronary CTA) are all given a “may be appropriate” rating. This publication (97) emphasizes the concept that just because a test is rated “appropriate” or “may be appropriate,” does not mean that it must always be performed, and clinical judgment of the health-care professional always has its place (28). In asymptomatic people with diabetes without any previous cardiac event, screening for silent myocardial ischemia targeted to revascularization, has not been shown to provide benefits in terms of cardiac prevention. Widespread use of screening tests is not justified since it does not prevent first cardiac event (98). Thus, testing for the presence of CAD may modulate medical treatment (more aggressive risk factor management) but revascularization therapy has not been shown to alter outcomes in the asymptomatic person with type 2 diabetes except in people with decreased left ventricular ejection fraction but viable myocardium.

RECOMMENDATIONS

1. A resting ECG, repeated every 3 to 5 years, should be performed in individuals with diabetes with any of the following [Grade D, Consensus for all of the following]:
   a. Age >40 years
   b. Duration of diabetes >15 years and age >30 years
   c. End organ damage (microvascular, CV)
   d. ≥1 CVD risk factor(s) (current smoking, hypertension, family history of premature CVD in first degree relative [men <55 years, women <65 years], CKD, obesity [BMI >30 kg/m^2], erectile dysfunction)
   e. Age >40 years and planning to undertake very vigorous or prolonged exercise, such as competitive running, long-distance running, or high-intensity interval training (see Physical Activity and Diabetes chapter, p. S54).

2. People with diabetes should undergo investigation for CAD by exercise ECG stress testing as the initial test in the presence of any of the following:
   a. Typical or atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort) [Grade C, Level 3 (13)]
   b. Signs or symptoms of associated diseases
      i. PAD (abnormal ankle-brachial index) [Grade D, Level 4 (18)]
      ii. Carotid bruits [Grade D, Consensus]
      iii. Transient ischemic attack [Grade D, Consensus]
   c. Stroke [Grade D, Consensus]
   d. Resting abnormalities on ECG (e.g. Q waves) [Grade D, Consensus]
   e. CAC score >400 Agatston score [Grade D, Consensus].

3. Pharmacological stress echocardiography or nuclear imaging should be used in individuals with diabetes in whom resting ECG abnormalities preclude the use of exercise ECG stress testing (e.g. left bundle branch block or ST-T abnormalities) [Grade D, Consensus]. In addition, individuals who require stress testing and are unable to exercise should undergo pharmacological stress echocardiography or nuclear imaging [Grade C, Level 3 (40)].

4. Individuals with diabetes who demonstrate ischemia at low exercise capacity (<5 METs) on stress testing should be referred to a cardiac specialist [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *ACR*; albumin to creatinine ratio; *CAC*, coronary artery calcium; *CAD*, coronary artery disease; *CHD*, coronary heart disease; *CI*, confidence interval; *CKD*, chronic kidney disease; *CT*; computed tomography; *CTA*, computed tomography angiography; *CV*, cardiovascular; *CVD*, cardiovascular disease; *ECG*, electrocardiogram, *HDL-C*, high density lipoprotein cholesterol; *HR*, hazard ratio; *LDL-C*, low-density lipoprotein cholesterol; *MI*, myocardial infarction; *p*; probability; *PAD*, peripheral artery disease; *PVD*, peripheral vascular disease.

Author Disclosures

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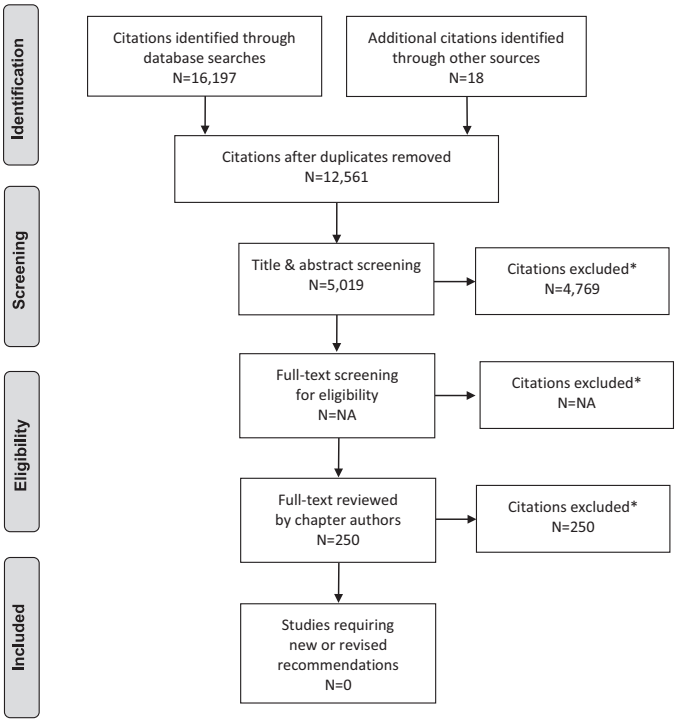
Literature Review Flow Diagram for Chapter 24: Screening for the Presence of Cardiovascular Disease



*Excluded based on: population, intervention/exposure, comparator/control or study design.

NA—not applicable.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (99).

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2018 Clinical Practice Guidelines

Dyslipidemia

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The beneficial effects of lowering low-density lipoprotein (LDL)-cholesterol with statin therapy apply equally well to people with diabetes as to those without the disease.
- The primary treatment goal for people with diabetes is LDL-cholesterol consistently <2.0 mmol/L or >50% reduction from baseline. Alternative targets and goals are non-high-density lipoprotein (non-HDL) cholesterol <2.6 mmol/L or apolipoprotein B <0.8 g/L. Achievement of the primary goal may require intensification of healthy behaviour interventions with statin monotherapy. On occasion, the addition of other lipid-lowering medications may be required.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Most adults with diabetes are at greater risk for cardiovascular diseases, such as heart attack and stroke.
- People with diabetes have an increased risk of cardiovascular diseases even if their LDL-cholesterol is "normal". They have an even higher risk if their LDL-cholesterol is elevated.
- Adults with diabetes should have their cholesterol tested yearly or as indicated by your health-care provider. More frequent testing may be necessary for people taking cholesterol medications.
- Always discuss your cholesterol results with your physician or nurse practitioner and other members of your health-care team.

Introduction

Diabetes is associated with a high risk of vascular disease (i.e. 2- to 4-fold greater risk than that of individuals without diabetes). In fact, cardiovascular disease (CVD) is the primary cause of death among people with type 1 and type 2 diabetes (1–3). Aggressive management of all CVD risk factors, including dyslipidemia, is, therefore, generally necessary in individuals with diabetes (4–6).

The most common lipid pattern in people with type 2 diabetes consists of hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C) and relatively normal plasma concentrations of low-density lipoprotein cholesterol (LDL-C). However, in the presence of even mild hyper-TG, LDL-C particles are typically small and dense and may be more susceptible to oxidation. In addition, chronic hyperglycemia promotes the glycation of LDL-C, and both glycation and oxidation are believed to increase the atherogenicity of LDL-C. Both of these processes may impair function and/or enhance atherogenicity even in those with type 1 diabetes with a normal lipid profile. The risk imparted by this lipid profile, even when LDL-C is considered low, remains quite substantial (7). Table 1 lists the components of dyslipidemia associated with diabetes (8,9). Many of these abnormalities also are seen in people with metabolic syndrome (10,11).

Table 1
Dyslipidemia components associated with type 2 diabetes and metabolic syndrome*

- Increased TG and TG-rich lipoproteins
- Increased postprandial TG
- Low HDL-C
- Low apo A-I
- Decreased small HDL, prebeta-1 HDL, alpha-3 HDL
- Increased apo B
- Increased LDL particle number
- Increased small, dense LDL
- Increased apo C-III
- Increased non-HDL-C
- Increased oxidized and glycated lipids

Apo, apolipoprotein; *HDL*, high-density lipoprotein; *HDL-C*, high-density lipoprotein cholesterol; *LDL*, low-density lipoprotein; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride.

* Adapted from reference 8.

Risk Assessment of Individuals with Diabetes

A detailed overview of risk assessment to guide decisions in whom to use statin therapy is provided in the Cardiovascular Protection in People with Diabetes chapter, p. S162. Principles of risk assessment also are discussed in the *2016 Canadian Cardiovascular Society (CCS) Guidelines for the Management of Dyslipidemia* (12,13), and efforts were made to ensure consistency between the guidelines. Accordingly, actual risk calculation is not required in most cases as people with diabetes >40 years of age, or >30 years of age and duration of diabetes >15 years or with concomitant microvascular or cardiovascular (CV) disease warrant therapy (13).

Screening

The burden of dyslipidemia is high in people with diabetes. A national cross-sectional chart audit study of 2,473 Canadians with type 2 diabetes revealed that 55% of individuals with a diabetes

Conflict of interest statements can be found on page S183.

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diagnosis of 2 years' duration also had dyslipidemia. This proportion rose to 66% in those with diabetes for 15 years (14). Therefore, a fasting lipid profile (total cholesterol [TC], HDL-C, TG and calculated LDL-C) should be conducted at the time of diagnosis of diabetes and if treatment is not warranted, the assessment should be repeated annually or as clinically indicated. If treatment for dyslipidemia is initiated, more frequent testing is warranted.

A fast of >8 hours may be inappropriate for individuals with diabetes, especially if long-acting basal insulin is part of their treatment regimen. Although nonfasting LDL-C is generally valid unless TG is elevated, non-HDL-C (defined as TC minus HDL-C) or apolipoprotein B (apo B) measurements (see below) are also valid even in the nonfasting state and even if the TG level is not normal. Indeed, the most recent CCS guidelines for management of dyslipidemia now endorse the option of nonfasting lipid measurements more broadly, not solely in people with diabetes, unless the person is known to have abnormalities of TG. Laboratories will not report LDL-C when TG is ≥4.5 mmol/L. In people known to have this level of hypertriglyceridemia, a fasting profile should be performed but non-HDL-C or apo B may still need to be used to determine atherogenicity of the dyslipidemia in this circumstance as well (13). For screening in children and adolescents, please refer to the chapters dedicated to diabetes in these groups (Type 1 Diabetes in Children and Adolescents chapter, p. S234; Type 2 Diabetes in Children and Adolescents chapter, p.S247).

Healthy Behaviour Interventions

Healthy behaviour interventions remain a key component of CVD prevention strategies and of diabetes management in general. Achievement of healthy weight and aerobic activity level, adoption of an energy-restricted, compositionally well-balanced diet that is low in cholesterol, saturated and trans fatty acids and refined carbohydrates, inclusion of viscous fibres, plant sterols, nuts and soy proteins, use of alcohol in moderation and smoking cessation all are fundamental considerations to improve glycemic control, the overall lipid profile and, most importantly, to reduce CVD risk (15–26). Each of these is discussed in more detail in accompanying chapters (Physical Activity and Diabetes chapter, p. S54; Nutrition Therapy chapter, p. S64; Weight Management in Diabetes chapter, p. S124).

LDL-C

A number of studies and meta-analyses have shown that the degree of LDL-C lowering with statins and the beneficial effects of lowering LDL-C apply equally well to people with and without diabetes (27–38). Large trials have demonstrated the benefits of statin therapy in both the primary and secondary prevention of CVD, and subgroup analyses of these studies have shown similar benefits in subsets of participants with diabetes (28–30,39). Across all subgroups, statin therapy provides the same relative risk reduction in terms of outcomes, but the absolute benefit depends on the baseline level of absolute risk, which is typically increased in people with diabetes. Subgroup analyses from statin trials also have shown similar relative benefits of LDL-C lowering, regardless of baseline LDL-C (30,32).

Intensive-dose statin has been demonstrated to improve outcome compared to moderate-dose statins, even in older people with MI or in people on dialysis (40–43). Therefore, statin use should be considered for any person with diabetes at risk of a CV event. In the very small group of lower-risk individuals with type 2 diabetes, the relative reduction in CVD risk with statin therapy is likely to be similar to that seen in those at higher global risk for CVD, but the absolute benefit from statin therapy is predicted to be smaller. However, the global CVD risk of these individuals is lifelong, will increase with age and may be worsened in the presence of additional CV risk factors. Therefore, repeated monitoring of the CVD risk status of people with diabetes (as outlined in the screening section above) is recommended.

The results of the Heart Protection Study (HPS), which compared simvastatin 40 mg daily to placebo, provide considerable insight into the importance of LDL-C lowering in the general population and, in particular, among people with diabetes (31). In the overall study, involving >20,000 participants, similar risk-ratio reductions were observed in participants with baseline LDL-C >3.5 mmol/L, 3.0 to 3.5 mmol/L and <3.0 mmol/L. In the subgroup with diabetes (n=5,963, including 615 people with type 1 diabetes), treatment with 40 mg simvastatin daily resulted in a 27% reduction in CV events and a 25% reduction in stroke relative to treatment with placebo. The risk reduction was similar in the cohorts with and without diabetes, and the treatment benefit was independent of baseline HDL-C and LDL-C levels (LDL-C <3.0 mmol/L or ≥3.0 mmol/L), sex, vascular disease, type of diabetes (type 1 vs. type 2) and A1C level (30). These results emphasized the benefits of statin treatment irrespective of the pre-existing serum LDL-C level.

The Collaborative Atorvastatin Diabetes Study (CARDS) was the first completed statin trial to be conducted exclusively in people with type 2 diabetes without known CVD (32). The mean baseline LDL-C of the study population was 3.1 mmol/L, and all participants had at least 1 CVD risk factor in addition to diabetes. CARDS demonstrated that treatment with atorvastatin 10 mg daily was safe and highly efficacious in reducing the risk of a first CV event, including stroke. Treatment resulted in a mean LDL-C of 2.0 mmol/L and was associated with a reduced risk for CV events and stroke of 37% and 48%, respectively. These study findings support the value of treating even so-called "normal" LDL-C levels in people with type 2 diabetes and no known CVD. This concept is concordant with a recent analysis of CVD risk in adults with diabetes and LDL-C <2.6 mmol/L (7).

As mentioned previously, all CARDS subjects had at least 1 additional CVD risk factor (i.e. history of hypertension, retinopathy, microalbuminuria or macroalbuminuria, or current smoking), a profile that applies to an estimated 70% to 80% of people with type 2 diabetes (32,44). Results from the United States (US) Third National Health and Nutrition Examination Survey (NHANES III) indicate that 82% of people with diabetes and no clinically evident coronary artery disease (CAD) have at least 1 of the CARDS entry criteria risk factors (32). The CARDS investigators concluded that the study findings "challenge the use of a particular threshold level of LDL-C as the sole arbiter of which individuals with type 2 diabetes should receive statin therapy". The absolute risk, determined by other risk factors in addition to LDL-C, should drive the target levels (32,45). Indeed, the investigators questioned whether any individual with type 2 diabetes can be considered at sufficiently low risk for therapy to be withheld (32). A sub-analysis of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) revealed similar benefits of atorvastatin 10 mg vs. placebo in people with type 2 diabetes, hypertension and at least 3 additional risk factors (46).

The Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) assessed the effect of atorvastatin 10 mg daily vs. placebo on CVD prevention in 2,410 people with type 2 diabetes (47). Although originally designed as a secondary prevention trial, the protocol underwent several changes, including the addition of participants without known CAD and the eventual conversion of all participants with known CAD to open-label, lipid-lowering medication. Over the 4-year study period, mean LDL-C was reduced by 29% in the atorvastatin group compared to placebo ($p<0.0001$). The composite primary endpoint was reduced by 13.7%; however, this finding was not statistically significant and was generally considered to be

related to the methodological limitations of the study design and the protocol changes.

In the subgroup with diabetes (n=1,051) of the Treating to New Targets (TNT) trial conducted in individuals with stable CAD, those participants treated with atorvastatin 80 mg daily who achieved a mean LDL-C of 2.0 mmol/L had 25% fewer major CVD events than did those treated with atorvastatin 10 mg daily who achieved a mean LDL-C of 2.5 mmol/L (p=0.026) (34). Intensive therapy with atorvastatin 80 mg daily also reduced the rate of all CVD and cerebrovascular events compared to atorvastatin 10 mg daily. Notably, an increased event rate for all primary and secondary efficacy outcomes was noted in the subgroup with diabetes compared to the overall study population. This finding provides yet further evidence that people with diabetes and CAD are at extremely high risk of subsequent CVD events.

The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis of >170,000 statin-treated subjects found that for every 1.0 mmol/L reduction in LDL-C, there was an approximately 20% reduction in CVD events, regardless of baseline LDL-C (48). The proportional reductions were very similar in all subgroups, including those with diabetes without pre-existing vascular disease (48). In fact, the CTT meta-analysis of >18,000 participants with diabetes from 14 randomized statin trials found that the effects of statins on all fatal and nonfatal CV outcomes were similar for participants with or without diabetes (49). The updated CTT meta-analysis of 170,000 participants showed that additional reductions in LDL-C (down to approximately 1.0 to 2.0 mmol/L) with more intensive therapy further reduced the incidence of major vascular events and that these reductions could be achieved safely, even in individuals with lower baseline LDL-C levels (50). The IMproved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that the addition of ezetimibe to simvastatin in participants with recent acute coronary syndrome imparted an incremental CVD event benefit compared to use of simvastatin alone and the magnitude of the event reduction was commensurate with the degree of additional LDL-C lowering imparted by ezetimibe. The mean LDL-C in the simvastatin plus ezetimibe arm was 1.4 mmol/L and 1.8 mmol/L in the simvastatin-treated cohort. The event reductions were particularly evident in people with type 2 diabetes (39).

Although the linear relationship between the proportional CVD risk reduction and LDL-C lowering would suggest that there is no lower limit of LDL-C or specified LDL-C target (as the CTT authors suggest), the clinical trial evidence summarized above would suggest that LDL-C consistently <2.0 mmol/L is currently the most appropriate target for high-risk individuals. In the vast majority of people, this target can be achieved with either a statin alone or a statin in combination with another lipid-lowering agent, such as ezetimibe, as shown in the IMPROVE-IT trial (39). People with diabetes and renal dysfunction or those requiring dialysis constituted 23% of the study population of the Study of Heart and Renal Protection (SHARP) trial. The study showed that LDL-C reductions with simvastatin plus ezetimibe were associated with reductions in the incidence of major atherosclerotic events vs. placebo. Subgroup and heterogeneity analysis revealed no difference in risk reduction between participants with or without diabetes using the statin/ezetimibe combination (51). A population-based cohort study suggests that the statin/ezetimibe combination is associated with lower rates of major adverse cardiac events in type 2 diabetes than high potency statins alone (52). These observations suggest that if statin alone does not achieve the expected LDL-C lowering effect desired, the statin/ezetimibe option should be considered.

Of particular interest is the recent availability of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors which are now indicated for use in people with either familial hypercholesterolemia or clinical atherosclerotic CVD who are not achieving LDL-C goals with healthy behaviour interventions, including diet and exercise and maximally tolerated statins. People with diabetes who also have these features should be considered candidates for these agents as per CCS recommendations (13). Subgroup analyses of these phase 2 and 3 studies of these agents suggest that subjects with diabetes have similar improvements in their lipid profile as do people without diabetes. Indeed, the first pivotal, secondary prevention trial using a PCSK9 inhibitor (53) and a prespecified subgroup analysis of the participants with concomitant diabetes (54) demonstrate further risk reduction with the combination of statin plus PCSK9 inhibitor when compared to statin alone. Risk reductions in participants with or without diabetes were similar; in those with diabetes, the risk reduction in the composite endpoint of CV death, MI, stroke, hospitalization for unstable angina or revascularization was 23%. There was also an 18% reduction in the participants with diabetes in the composite endpoint of CV death, MI and stroke, a benefit that was similar to that experienced by participants without DM. In addition, there was no evidence of worsening of hyperglycemia in the participants with diabetes or of new onset diabetes in those without.

Table 2
First-line therapy to achieve a primary lipid target of LDL-C consistently less than 2.0 mmol/L

Statins*		
Generic name†	Tradename	Considerations
Atorvastatin	Lipitor® and generics	Statins are drugs of choice to lower LDL-C and have modest TG-lowering and HDL-C raising effects at higher doses.
Fluvastatin	Lescol®	
Lovastatin	Mevacor® and generics	
Pravastatin	Pravachol® and generics	
Rosuvastatin	Crestor® and generics	
Simvastatin	Zocor® and generics	

HDL-C, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride.
Note: Prescribers should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.
* Prevention of statin-induced myopathy requires attention to factors that increase risk, such as age >80 years (especially women); small body frame and frailty; higher dose of statin; multisystem diseases (e.g. chronic renal insufficiency due to diabetes); multiple medications; hypothyroidism; perioperative periods; alcohol abuse; excessive grapefruit juice consumption; and specific concomitant medications, such as fibrates (especially gemfibrozil) (refer to specific statin package inserts for others) (102,104,105).
† Listed in alphabetical order.

Tables 2 and 3 summarize considerations that should guide the choice of pharmacological agent(s) for the treatment of dyslipidemia. Although it has not been studied in any event-based randomized clinical trial, colesevelam, a bile acid sequestrant, appears to have an ancillary effect on lowering A1C (55,56).

People with IGT (particularly in the context of metabolic syndrome) are at significant risk for the development of CVD. Indeed, some studies suggest that their vascular risk is almost as high as individuals with existing type 2 diabetes (57,58) (see Cardiovascular Protection in People with Diabetes, p. S162). No clinical trials of lipid-lowering agents have been conducted exclusively in people with impaired glucose tolerance (IGT); however, given their increased CVD risk, it is reasonable to consider treating this population to the same targets as people with diabetes (59). To reduce the CVD morbidity and mortality associated with prediabetes and metabolic syndrome, an aggressive approach aimed at associated CVD risk factors, including dyslipidemia, is warranted. Healthy behaviour interventions aimed at reducing the risk of developing both type 2 diabetes and CVD are essential.

Additional lipid markers of CVD risk

The TC/HDL-C ratio is an index of CVD risk (60) and is considered to be a traditional determinant or risk marker when considering the need for lipid-lowering therapy. An elevated TC/HDL-C ratio is

Table 3
Other lipid-modifying medications

Drug class* Generic name* (tradename)	Principal effects	Other considerations
Bile acid sequestrants (BAS) • Cholestyramine resin (Questran®) • Colesevelam (Lodalis®) • Colestipol HCl (Colestid®)	• Lowers LDL-C	• GI intolerability, which worsens with increasing doses • May elevate TG • Colesevelam has A1C-lowering effect
Cholesterol absorption inhibitor • Ezetimibe (Ezetrol® and generics)	• Lowers LDL-C	• Less effective than statins as monotherapy • Effective when used in combination with a statin to further lower LDL-C (38,39)
Fibrates • Bezafibrate (Bezalip SR® and generic) • Fenofibrate (micronized/microcoated/nano crystals) (Lipidil Micro®, Lipidil Supra®, Lipidil EZ®, and generics) • Gemfibrozil (Lopid®)	• Lowers TG • Variable effect on LDL-C • Highly variable effect on HDL-C (more effective at raising HDL-C when baseline TG is high)	• May increase creatinine and homocysteine levels; however, favourable effects on renal function have been noted with long-term fenofibrate treatment (68); possible benefit of fenofibrate on retinopathy • Do not use gemfibrozil in combination with a statin due to increased risk of myopathy and rhabdomyolysis†
Nicotinic acid • Extended-release niacin (Niaspan®, Niaspan FCT®) • Immediate-release niacin (generic, nonprescription) • Long-acting (e.g. "no-flush") niacin (generic, nonprescription or niacin/laropiprant combinations) **not recommended**	• Raises HDL-C • Lowers TG • Lowers LDL-C • Lowers Lp(a)	• To be used selectively and cautiously but not to be used prior to trials of ezetimibe or BAS • Can cause dose-related deterioration of glycemic control • Long-acting niacin should **not** be used due to increased hepatotoxicity and decreased efficacy (106)
PCSK9 inhibitor • Alirocumab (Praluent®) • Evolocumab (Repatha®)	• Lowers LDL-C • Lowers Lp(a), also, modest TG-lowering and HDL-C raising effects	• Injection site reactions (107–110) • CV risk reduction shown in 1 randomized clinical trial of secondary prevention, including in a subset with type 2 diabetes

A1C, glycated hemoglobin; *BAS*, bile acid sequestrant; *CV*, cardiovascular; *GI*, gastrointestinal; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *Lp(a)*, lipoprotein(a); *PCSK9*, proprotein convertase subtilisin/kexin type 9; *TG*, triglyceride.
Note: Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.
* Listed in alphabetical order.
† See footnote to Table 2 regarding prevention of myopathy.

usually associated with a low HDL-C and/or elevated TG, both of which are commonly seen in individuals with diabetes and often in individuals without diabetes, even in the face of an optimal LDL-C (7). The elevated TC/HDL-C ratio is considered to represent a marker of lipid-derived, residual risk in treated patients, but it is not considered a target of therapy. Even so, this dyslipidemia is relatively responsive to healthy behaviour interventions (e.g. an increase in physical activity and weight reduction) and improvements in glycemic control, interventions that should be considered in all instances anyway.

To reduce the residual CVD risk despite statin therapy, the potential benefit of additional lipid modification of high TG or low HDL-C with adjuvant pharmacotherapy has attracted tremendous interest. However, 3 recent studies, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (cohort consisted exclusively of patients with diabetes), the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial, and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial highlight the importance of maintaining LDL-C lowering as the primary focus of treatment, particularly with statins (61–63). Fenofibrate was used in ACCORD and niacin was used in AIM-HIGH and HPS2-THRIVE. Both of these second-line adjunctive therapies failed to show any added clinical benefit compared to statin therapy alone. Therefore, neither niacin or fibrates can be recommended as routine adjunctive therapy in people already meeting LDL-C targets with statins since these agents appear to have no additional impact on CVD endpoints. In some people, however, these agents may help achieve LDL-C goals (13). The results of 4 recent meta-analyses examining the effects of fibrate therapy on CV outcomes found that fibrates may be particularly beneficial in people with atherogenic dyslipidemia, which is characterized by elevated TG, small LDL particles and reduced HDL-C (64–67).

Evidence suggests that fibrate therapy may help reduce the microvascular complications associated with diabetes (i.e. retinopathy and nephropathy), and it appears as if these beneficial effects are not solely due to the lipid changes induced by this drug class (68–70). For example, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that long-term treatment with fenofibrate reduced albuminuria and slowed estimated glomerular filtration rate loss over 5 years, despite initially and reversibly increasing plasma creatinine (68). Furthermore, if residual hyper-TG is high enough to impart a risk of pancreatitis, fibrates may be warranted.

Although TG is not a target of therapy for CV risk reduction, a TG level <1.5 mmol/L is considered optimal since, below this level, there are fewer associated metabolic abnormalities, such as low HDL-C, small dense LDL particles and postprandial lipemia (36,71–74). As indicated above, healthy behaviour interventions, including healthy eating, weight management and improved glycemic control, should all be emphasized.

While several studies have shown that fibrate therapy is associated with CVD prevention, there is much less evidence for CVD risk reduction with fibrates relative to statins, specifically in people with diabetes (75–79). In some studies, no statistically significant reduction in the primary endpoint was demonstrated with fibrate therapy (80,81). Combination therapy with fenofibrate (82,83) or bezafibrate plus a statin appears to be relatively safe if appropriate precautions are taken (Tables 2 and 3). But, as discussed above, the efficacy of these approaches in improving patient outcomes has not been established (61). Although combination treatment with fenofibrate appears to be safe (61,80), statins should not be used in combination with gemfibrozil due to an increased risk of myopathy and rhabdomyolysis (84).

To reduce the risk of pancreatitis rapidly, a fibrate is recommended for individuals with fasting TG levels >10.0 mmol/L who do not respond to other measures, such as intensified glycemic control, weight loss and restriction of refined carbohydrates and alcohol (85). When there is no overriding concern for acute pancreatitis and when there is evidence of hyper-TG in association with

an elevated apo B or high non-HDL-C, it would be reasonable to consider a statin as first-line therapy with the subsequent addition of a fibrate, as needed.

As discussed above, evidence has emerged to support the use of apo B determination in the management of patients with dyslipidemia (12,13,45). Mechanistically, it is important to consider that there is 1 apo B molecule per LDL-lipoprotein (a) [Lp(a)], very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) particle, all of which are atherogenic. Apo B has repeatedly been shown to be a better risk marker for CVD events than LDL-C. Consequently, the measurement of apo B and its monitoring in response to lipid-lowering therapy have been advocated by some authors (12,13,45,86). The measurement of apo B is most clinically useful in the individual with hyper-TG since it provides an indication of the total number of atherogenic lipoprotein particles in the circulation through direct measurement, as opposed to calculated LDL-C which cannot be determined reliably with TG above 4.5 mmol/L and which will be systematically underestimated even when TG are 1.5 to 4.5 mmol/L. Because hyper-TG is commonly seen in people with diabetes, a focus on non-HDL-C or measurement of the apo B level can be used to guide therapy. Based on available evidence, an optimal level of apo B can be considered to be at least <0.9 g/L (87) or, as supported by the CARDS study in subjects with diabetes, <0.8 g/L (45). The latter threshold is endorsed by the Canadian Cardiovascular Society (13).

Further important information has emerged from CARDS with respect to alternative targets and therapeutic goals (32). In an extensive analysis of both spontaneous and statin-induced changes in LDL-C, apo B concentrations and non-HDL-C, outcomes were found to be more consistently related to apo B during statin treatment than LDL-C or non-HDL-C (45). In people treated with a statin, the average apo B concentration in the subgroup with concomitant LDL-C of 2.0 mmol/L was 0.708 g/L, with an upper 95% confidence limit of 0.720 g/L.

The calculated non-HDL-C (TC minus HDL-C) has features similar to apo B: the calculation is valid in the nonfasting state, and it relates mainly to cholesterol contained in atherogenic particles, each of which has an apo B [atherogenic particles, such as VLDL and IDL, LDL, and Lp(a)]. A linear relationship between apo B and non-HDL-C exists over a broad range (88). A non-HDL-C level of 2.6 mmol/L is approximately equal to an apo B of 0.8 g/L and both may be considered alternate goals of therapy. It should be recognized, however, that sole reliance on this general correlation would imply that all people have an average size of LDL-C which is clearly not the case. Thus, these correlations apply to populations and not necessarily to individual patients as LDL-C particle size may vary substantially, leading to the observed standard error associated with the linear correlation. But since non-HDL-C is available without additional cost or separate assay, it is attractive to consider, and its clinical use is supported by several analyses (89–91).

Apo A-I is the defining protein of HDL and is a surrogate marker of the number of HDL particles in the circulation. The relationship between apo A-I and HDL-C is more complicated than the 1:1 relationship of the number of apo B molecules and atherogenic particles because there may be 2 to 4 apo A-I molecules per HDL particle. The apo B/apo A-I ratio has been proposed to be the best single predictor of CVD risk, accounting for 50% of population-attributable events in an ethnically diverse population without diabetes, which was higher than the 32% population attributable risk seen with TC/HDL-C ratio in this study sample (92,93). Currently, in Canada, however, the measurement of apo A-I is even less widely available and less standardized than apo B, thus limiting the practical value of both this measurement and the apo B/apo A-I ratio for clinical decision making.

Finally, because of a series of conflicting results from biochemical and genetic studies of HDL, and several apparently failed clinical trials that aimed to reduce CVD events by pharmacologically raising HDL (94), there has been reconsideration of the targeting of HDL-C. As a predictor, HDL-C and the derived TC/HDL-C ratio are excellent, but it is now clear that HDL-C is not automatically a good target for therapy. The future status of targeting HDL-C or alternative ways of measuring HDL function is a subject of active debate and investigation.

In summary, in order to reduce CVD risk among individuals with diabetes, it is important to understand the atherogenicity of small, dense LDL particles, remnant lipoproteins, TG-rich particles and the complex anti-atherogenic role of HDL particles. It is paramount to improve these metabolic parameters primarily through healthy behaviour interventions, improved glycemic control and pharmacotherapy, when indicated. Despite academic interest in various lipid parameters, it is of paramount importance to realize that the current best-outcome evidence for minimizing the atherogenic impact of lipid abnormalities in people with diabetes is to remain focused on achieving very low plasma concentrations of LDL-C, typically with statin-based therapy, as this conclusion is based on the most extensive clinical trial evidence. For people who are not at goal, despite maximally tolerated statin therapy or in the case of statin intolerance, the use of second-line LDL-C-lowering therapies (Tables 2 and 3) can be considered (95).

Statin Therapy and Incident Diabetes

Although statins are the cornerstone of lipid-altering therapy for CVD risk reduction in people with or without diabetes, recent evidence has suggested that chronic statin use is associated with an increased risk of incident diabetes. The interplay between statin therapy and incident diabetes was highlighted in a prespecified analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), which actually showed a decrease in the incidence of new-onset diabetes with pravastatin therapy (96). In contrast, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) showed an increase in incident diabetes with rosuvastatin (97). Several meta-analyses suggest that there is indeed a small overall increase in diabetes with chronic statin use (98,99) and that this risk may be related to the statin dose (100). The mechanistic link appears to involve inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (101). Although this finding is of little relevance to people with established diabetes, it may be of relevance to people who are at risk for developing diabetes irrespective of statin treatment, such as those who have obesity and/or who manifest metabolic syndrome. However, as discussed earlier, even people with risk factors for the development of diabetes enjoy a marked benefit in CVD risk reduction through the LDL-C lowering effects of statins, which appears to far outweigh any small risk of new-onset diabetes (57,58). Accordingly, these recent analyses do not affect the recommendation that statins are the preferred agents for lowering LDL-C in most instances, including in people with established diabetes or in those with risk factors for developing the disease (102,103).

RECOMMENDATIONS

1. A lipid profile (i.e. TC, HDL-C, TG, calculated LDL-C and/or apo B, or non-HDL-C), fasting or nonfasting, should be measured routinely. In those with known TG >4.5 mmol/L, a fasting (>8-hour fast) lipid profile should be performed. If lipid-lowering treatment is not initiated, a lipid profile should be repeated every 1 to 3 years based on CV risk. Repeat testing should be performed 3 to 6 months after treatment for dyslipidemia is initiated to verify lipid targets are being met [Grade D, Consensus for all statements].

2. For people with diabetes with indications for lipid-lowering therapy (see Cardiovascular Protection in People with Diabetes chapter, p. S162), treatment should be initiated with a statin [Grade A, Level 1 (30,32)] to achieve LDL-C consistently <2.0 mmol/L [Grade C, Level 3 (51)] or >50% reduction of LDL-C from baseline [Grade D, Consensus]. Alternative targets and respective goals are apo B <0.8 g/L and non-HDL-C <2.6 mmol/L [Grade C, Level 3 (49)].

3. In people with diabetes achieving LDL-C goal with statin therapy, fibrates or niacin should not be routinely added for the sole purpose of further reducing CV risk [Grade A, Level 1 (61–63)].

4. For individuals not at LDL-C goal despite statin therapy as described above, a combination of statin therapy with second-line agents may be used to achieve the goal and the agent used should be selected based upon the size of the existing gap to LDL-C goal [Grade D, Consensus]. Generally, ezetimibe should be considered [Grade D, Consensus]. In people with diabetes who also have concomitant clinical CVD, ezetimibe or evolocumab may be used to further reduce major adverse cardiac events [Grade A, Level 1 (39) for ezetimibe; Grade A, Level 1 (54) for evolocumab], and they should also be considered in those with concomitant familial hypercholesterolemia [Grade D, Consensus for ezetimibe and PCSK9 inhibitor].

5. For individuals with diabetes with fasting serum TG >10.0 mmol/L, a fibrate should be used to reduce the risk of pancreatitis [Grade D, Consensus] while also optimizing glycemic control and implementing healthy behaviour interventions (e.g. weight management, optimal dietary strategies, reduction of alcohol) [Grade D, Consensus].

Abbreviations:
apo B, apolipoprotein B; *apo A-I*, apolipoprotein A-I; *CAD*, coronary artery disease; *CV*, cardiovascular; *CVD*, cardiovascular disease; *HDL-C*, high-density lipoprotein cholesterol; *hyper-TG*, hypertriglyceridemia; *IGT*, impaired glucose tolerance; *LDL-C*, low-density lipoprotein cholesterol; *MI*, myocardial infarct; *non HDL-C*, non-high-density lipoprotein cholesterol; *PCSK9*, proprotein convertase subtilisin/kexin type 9; *TC*, total cholesterol; *TG*, triglycerides.

Other Relevant Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, p. S10
Physical Activity and Diabetes, p. S54
Nutrition Therapy, p. S64
Weight Management in Diabetes, p. S124
Cardiovascular Protection in People with Diabetes, p. S162
Screening for the Presence of Cardiovascular Disease, p. S170
Treatment of Hypertension, p. S186
Management of Acute Coronary Syndromes, p. S190
Treatment of Diabetes in People With Heart Failure, p. S196
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247

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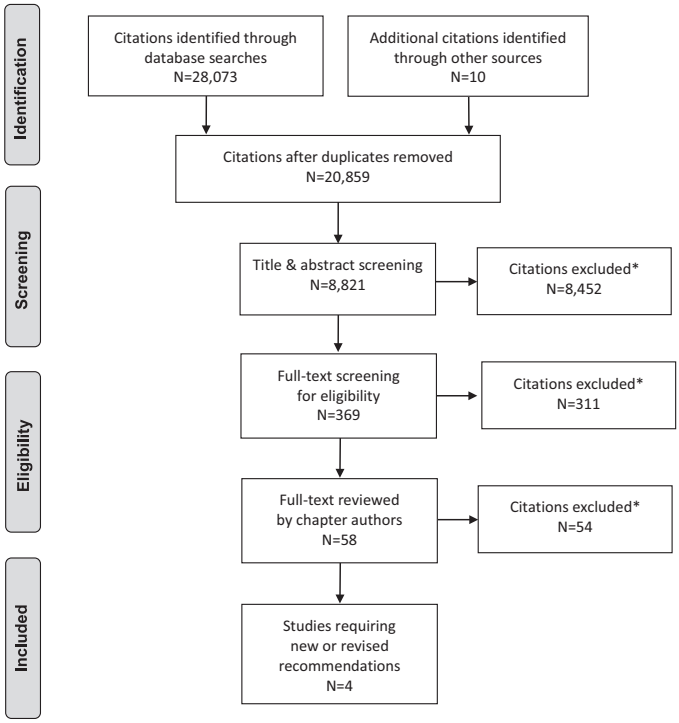
Literature Review Flow Diagram for Chapter 25: Dyslipidemia



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Treatment of Hypertension

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- People with diabetes should be treated to achieve a BP <130/80 mmHg.
- For persons with cardiovascular disease or chronic kidney disease, including albuminuria, or with cardiovascular risk factors in addition to diabetes and hypertension, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker is recommended as initial therapy.
- Healthy behaviour interventions are supplementary to pharmacologic therapy and consist of reducing excess body weight, reducing sodium intake toward (2,000 mg/day), increasing consumption of fruits and vegetables (8 to 10 servings per day), low-fat dairy products (2 to 3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) and increasing physical activity levels.
- Most people with diabetes should receive standard-dose monotherapy for initial management of hypertension; however, there is emerging evidence for supporting earlier use of single pill combination therapy.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- It is important to have your blood pressure checked regularly.
- Have your blood pressure checked at least once every year by a health-care provider or more often if your blood pressure is high.
- You can also check your blood pressure at home. If home blood pressure readings are done properly, they may reflect your usual blood pressure more than those done in the health-care provider's office.
- For most people with diabetes, blood pressure should be less than 130/80 mmHg.
- Patient resources on hypertension are available at Hypertension Canada (http://guidelines.hypertension.ca/patient-resources/).

Introduction

Observational and randomized clinical trials and observational data show a strong association between raised systolic and diastolic blood pressures (BPs) and clinically important microvascular (e.g. retinopathy and nephropathy) and cardiovascular (CV) complications in people with hypertension who have diabetes mellitus. The association between BP level (systolic and diastolic) and CV risk is continuous and graded in people with diabetes. Treatment of hypertension appears to confer greater benefits in people with diabetes than in age-matched people with hypertension who do not have diabetes (1–3). The benefits of intensive BP lowering may even exceed those of intensive glycemic control in people with diabetes mellitus for the prevention of CV complications (4,5). Because cardiovascular disease (CVD) is the most common cause of death in people with diabetes mellitus (6), BP control is paramount.

Blood Pressure Targets

In participants with diabetes, there is randomized clinical trial evidence supporting lower BP levels (2 major trials are the United Kingdom Prospective Diabetes Study Group (UKPDS)-38 trial and the Hypertension Optimal Treatment (HOT) trial) (4,7). In the UKPDS-38 trial, more intensive BP lowering led to reductions in risk of microvascular diabetic endpoints of 37% (95% confidence interval [CI] 11–56) and in stroke of 44% (95% CI 11–65) (4). In the treat-to-target HOT trial, within the a priori-specified subgroup of people with diabetes, the rate of major CV events was 51% lower in participants randomly assigned to achieve target BPs <80 mmHg than in subjects with target pressures of 85 to 90 mmHg (7). Therefore, the HOT trial results support a diastolic BP treatment goal of ≤80 mmHg.

Use of combination therapy is supported by the results of the BP-lowering arm of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (8). In this trial, 11,140 participants with type 2 diabetes >55 years of age with a history of major CVD or CV risk factors were randomly assigned to receive perindopril/indapamide vs. placebo in addition to current antihypertensive therapy (8). After a mean follow-up period of 4.3 years, combination therapy was associated with a 5.6/2.2 mmHg greater reduction in BP compared with placebo. There were no significant differences in the CV or microvascular primary endpoints between combination therapy and placebo. In the secondary endpoint analysis, however, combination therapy was associated with a significant reduction in CV death (hazard ratio [HR] 0.82, 95% CI 0.68–0.98, p=0.03) and total mortality (HR 0.86, 95% CI 0.75–0.98, p=0.03) compared with placebo. Rates of serious adverse events and permanent discontinuation for hypotension or dizziness were similarly low in combination and placebo groups. Several trials in people without diabetes also found combination therapy to be associated with greater BP lowering, reduced rates of CV endpoints and low rates of adverse events (9,10). Given the significantly greater BP reductions associated with combination therapy, a combination of 2 first-line agents should be used

Conflict of interest statements can be found on page S188.

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in people with significant elevations in BP. Caution, however, should be exercised in people in whom a substantial fall in BP is more likely to occur or is more poorly tolerated (e.g. the elderly, people with active CAD and people with autonomic neuropathy).

The recommendation to lower systolic BP to <130 mmHg is partly based on prospective cohort data; specifically, the Pittsburgh Epidemiology of Diabetes Complications Study (in people with type 1 diabetes mellitus) and the UKPDS-36 (in people with type 2 diabetes) demonstrated a linear relationship between systolic BP levels and mortality, CAD, overt diabetic nephropathy and proliferative retinopathy (11,12). These associations were maintained even after adjustment for other confounding factors (such as lipid levels, age, sex and glycemic control). In these studies, direct relationships were seen between the magnitude of incremental BP reduction and reductions in risk of hypertension-related complications, over time.

Recent studies have led a re-evaluation of the systolic BP target of 130 mmHg. To a large extent, this has been precipitated by the findings of the Action to Control Cardiovascular Risk in Diabetes-Blood Pressure (ACCORD BP) trial in 2010 which compared the effects of targeting a systolic BP <140 mmHg with that of <120 mmHg (13). The primary outcome, a composite of myocardial infarction (MI), stroke and CV death was neutral, showing no significant difference between the 2 BP groups. These findings and the occurrence of more adverse effects in the lower target group, prompted guideline groups in the United States and Europe to move their threshold for initiation of antihypertensive therapy from 130 mmHg to 140 mmHg (14,15).

On further scrutiny, as noted in a review on the subject by Hypertension Canada and Diabetes Canada (16), the findings of the ACCORD BP trial are not quite as clear-cut as they seem at first glance. Notably, while the primary endpoint was neutral, stroke, a prespecified outcome in ACCORD BP, was reduced by 41% in the group with a <120 mmHg target (13). In addition, ACCORD BP may well have been underpowered, accruing an event rate that was only half of that anticipated. Moreover, a factorial designed study, such as ACCORD, assumes the absence of interaction between its interventions where $p<0.1$ is viewed as statistically significant (17). Notably, the probability of interaction between the glycemia and BP interventions in ACCORD BP was $p=0.08$, suggesting that the response to BP lowering may have been different between those randomized to usual vs. intensive glycemic control.

In the years that followed, the disclosure of the ACCORD BP findings, several meta-analyses and systematic reviews exploring BP thresholds and targets in diabetes have been published (18–21). In general, these concluded that there was little, if any, additional reduction in cardiac events by achieving systolic BP <140 mmHg. While one of these meta-analyses reported an association with CV death and the initiation of antihypertensive therapy in individuals with systolic BP <140 mmHg (21), this was not seen in the other analyses (18–20).

Although far less common than MI, but with devastating effects that make it especially feared by people, it may be argued that stroke warrants separate consideration. In addition to the ACCORD BP study that showed substantial stroke reduction with lower systolic BP (13), the meta-analyses detailed above also showed that while the other components of major adverse cardiac events were not improved, lowering BP <130 mmHg conferred additional protection against stroke (18–21).

Finally, although the Systolic Blood Pressure Intervention Trial (SPRINT) (22) and ACCORD BP (13) were different in their study of individuals without, and with, diabetes, respectively, they each examined similar BP targets in those at high CV risk. As such, it has been reasoned that they might be considered together rather than separately, arguing that a lower systolic BP target is appropriate in high-risk individuals whether they have diabetes or not (23). Taking all these factors into consideration, it is felt that there are insufficient data to recommend a change from the existing targets and treatment thresholds of a systolic BP target of <130 mmHg and diastolic BP target <80 mmHg.

Role of ACE Inhibitors and ARBs

These guidelines identify specifically those people with diabetes, and those people with evidence of increased urinary albumin excretion, as persons at high risk for CV events. In addition, the recommendations also recognize those people with known CVD, renal disease or elevated urinary albumin excretion, as well as those people with additional CV risk factors to be high-risk people who should receive an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy (see Cardiovascular Protection in People with Diabetes chapter, p. S162). This risk-assessment strategy is consistent with long-standing recommendations by both Hypertension Canada and Diabetes Canada that are based on multiple, large scale randomized controlled trials (24,25).

Antihypertensive Choices

Using ACE inhibitors or ARBs as first-line therapeutic agents is appropriate for persons at high risk for CV events. Based on publication of the diabetes subgroup results from the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (26), dihydropyridine calcium channel blockers (CCBs) were added to the list of potential first-line agents for persons with diabetes and with normal urinary albumin excretion (<30 mg/day). In the ALLHAT study subgroup, 13,101 participants with type 2 diabetes were randomly assigned to chlorthalidone, amlodipine or lisinopril. Although systolic BP was significantly lower among those participants randomly assigned to chlorthalidone compared with lisinopril or amlodipine, no difference was shown in primary endpoint of combined fatal coronary heart disease or non-fatal or fatal MI (HR 0.97, 95% CI 0.86–1.10) between amlodipine and chlorthalidone. While this lack of difference was consistent generally for other CV secondary endpoints, the study was underpowered to detect differences in development of end stage renal disease (ESRD). Thus, the proviso was added that ACE inhibitors and ARBs also appear to have renal benefits beyond that expected from their BP-lowering effects; therefore, health-care providers may wish to consider these additional benefits when selecting first-line agents.

Role of Combination Therapy

If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For persons in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic. The recommendation supporting ACE/CCB combination therapy in people with type 2 diabetes is based on the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, which compared benazepril/amlodipine combination treatment vs. benazepril/thiazide therapy (27). The primary endpoint was a composite of MI, stroke, CV death, hospitalization for angina, resuscitated cardiac arrest and coronary revascularization. The trial enrolled 6,946 high-risk participants with type 2 diabetes; 2,842 participants were deemed to be particularly “high risk” by virtue of a previous cardiac, cerebrovascular or renal event. Benazepril/amlodipine reduced occurrence of the primary event compared to benazepril/thiazide in all subjects with diabetes (8.8 vs. 11%; HR 0.79, 95% CI

0.68–0.92) and subgroups of subjects who were considered high risk (13.6 vs. 17.3%, HR 0.77, 95% CI 0.64–0.93).

Single pill combination therapy (SPC) is recommended as an initial treatment option to facilitate the achievement of lower blood pressures, to improve CV outcomes, promote adherence, and reduce medication side effects, relative to using maximal dose monotherapy (28). The improved therapeutic efficiency and efficacy of SPCs were documented in adults in the Heart Outcomes Prevention Evaluation-3 study where one-third had hypertension, 6% had early diabetes and 12% had impaired fasting or impaired glucose tolerance (29). While there is insufficient evidence at this time to make a strong recommendation for the use of SPCs in adults with diabetes, the benefits documented in other hypertensive populations is noteworthy. Historically, the early use of combination therapy was encouraged only in the context of significantly elevated BP (i.e. >20 mmHg above systolic target, or >10 mmHg above diastolic target), but given the evolving evidence for early use of SPCs, the tight linkage of combination therapy to degree of blood pressure elevation warrants re-evaluation.

Harmonization with Hypertension Canada

This chapter was completed in accordance with a memorandum of understanding with Hypertension Canada to produce harmonized guidelines for the management of hypertension in adults with diabetes. The methods used in this chapter were as per the Hypertension Canada Guidelines Committee and have been published previously (30). In brief, annual literature reviews were performed from 2013 to the present by a Cochrane-trained librarian searching for evidence on the management of hypertension in people with diabetes. Each abstract was reviewed by at least 2 people with concordance on the articles put forward for review to update the guidelines. These articles were assessed by a committee of experts whose conflicts of interest are listed with Diabetes Canada and Hypertension Canada, and recommendations passed on to the Central Review Committee. This committee of epidemiological experts, with no conflicts of interest, reviewed the recommendations and presented these at the Hypertension Canada consensus meeting, to stakeholders and, finally, to the Steering Committee of the Diabetes Canada 2018 Clinical Practice Guidelines.

RECOMMENDATIONS

1. People with diabetes mellitus should be treated to attain systolic BP of <130 mmHg [Grade C, Level 3 (11)] and diastolic BP of <80 mmHg [Grade B, Level 1 (7)] (these target BP levels are the same as BP treatment thresholds).

2. For people with CVD or CKD, including albuminuria, or with CV risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy [Grade A, Level 1A (31–34)].

3. For people with diabetes and hypertension not included in other recommendations in this section, appropriate choices include (in alphabetical order): ACE inhibitors [Grade A, Level 1A (26), ARBs [Grade A, Level 1A (29), dihydropyridine CCBs [Grade A, Level 1A (26), and thiazide/thiazide-like diuretics [Grade A, Level 1A (26)].

4. If target BP levels are not achieved with standard-dose monotherapy, additional antihypertensive therapy should be used. For people in whom combination therapy with an ACE inhibitor is being considered, a dihydropyridine CCB is preferable to a thiazide/thiazide-like diuretic [Grade A, Level 1A (26)].

Abbreviations:
ACE, angiotensin converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CCB,* calcium channel blocker; *CI,* confidence interval; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *HR,* hazard ratio; *MI,* myocardial infarction; *SPC,* single pill combination.

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2018 Clinical Practice Guidelines

Management of Acute Coronary Syndromes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Over the past 20 years, the rates of acute myocardial infarction in people with diabetes has decreased substantially. However, the burden of disease remains high because of the increased prevalence of diabetes.
- Diabetes and hyperglycemia are independent predictors of increased short- and long-term mortality, recurrent myocardial infarction, and the development of heart failure in patients with acute myocardial infarction.
- People with an acute myocardial infarction and hyperglycemia (random blood glucose >11.0 mmol/L) may receive antihyperglycemic therapy to maintain blood glucose levels between 7.0 to 10.0 mmol/L.
- People with diabetes are less likely to receive recommended treatment, such as an early invasive strategy and revascularization, reperfusion therapy, beta blockers or dual antiplatelet therapy than people without diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk person with myocardial infarction and diabetes.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- A heart attack can manifest as chest discomfort or crushing pain; or as pain in the arms, back, neck, jaw and, even, the stomach. Shortness of breath, cold sweat, nausea and lightheadedness may also occur.
- If you are experiencing symptoms of a heart attack, you should seek medical help immediately. The faster treatment is started, the better.

Introduction

Diabetes (together with lipid abnormalities, smoking and hypertension) is one of the top 4 independent risk factors for myocardial infarction (MI) (1). Today, approximately 15% to 35% of people admitted with an acute coronary syndrome (ACS) have known diabetes (2), and as many as a further 15% have undiagnosed diabetes (3). Between 1990 and 2010, there was a 67.8% reduction of the rates of acute MI in people with diabetes, compared to a 32% reduction in individuals without diabetes (4). However, as a result of the substantial increase in the prevalence of diabetes over this period, the public health burden of MI in people with diabetes continues to rise.

Compared to individuals without diabetes, people with diabetes have:

- A 3-fold increased risk of ACS (5)
- Occurrence of acute coronary events 15 years earlier (5)
- A 2-fold increased short- (6,7) and long-term mortality (6,8)
- An increased incidence of post-infarction recurrent ischemic events, heart failure and cardiogenic shock (3,9)
- A similar benefit from guideline-recommended management strategies (see below)
- Less utilization of guideline recommended care (10–13), including an invasive strategy (14) which may contribute to adverse outcomes (15).

Risk Stratification of People With Diabetes and ACS

It is recognized that there is a wide range of risk for an adverse outcome in people with diabetes after an ACS. A recent study developed a prediction model that indicated age, renal dysfunction, the presence of anemia, heart failure or left ventricular (LV) dysfunction, in-hospital revascularization, obesity, prior ACS and insulin treatment were factors significantly associated with mortality during the 5 years after acute MI (AMI) (16).

Identification of Diabetes in People with ACS

Although the absolute number of people with MI has fallen in the United States, the prevalence of diabetes in this population has steadily increased from 18% in 1997 to 30% in 2006 (16). More than two-thirds of people with MI have either diabetes or prediabetes (impaired glucose tolerance [IGT] or impaired fasting glucose [IFG]) (17). Abnormal glucose regulation is almost twice as prevalent in people with MI compared to a matched control population and is a marker for adverse outcomes (18). The frequency of previously unrecognized diabetes in the ACS population is reported to be between 4% and 22% depending on the test used for the diagnosis of diabetes (3,19). If fasting plasma glucose (FPG) criteria is used alone in the ACS population, diabetes is underdiagnosed in 39% compared to when the diagnosis is made from an oral glucose tolerance test (OGTT) (20). An A1C >6.5% is currently a diagnostic criterion for diabetes as it captures long-term glucose exposure, does not require fasting or timed samples and is currently used to guide management decisions (see Screening for Diabetes in Adults chapter, p. S16). One study has validated the use of A1C in an acute care population and found that using the 2-hour 75 g OGTT as a gold standard for the diagnosis of diabetes, and an A1C threshold of 6.0%, A1C had a sensitivity of 77% and a specificity of 87% (21). It is accepted that some people with diabetes will be missed by screening with fasting plasma glucose (FPG) and A1C compared to the universal use of an OGTT. However, it is likely that the people most in

Conflict of interest statements can be found on page S193.

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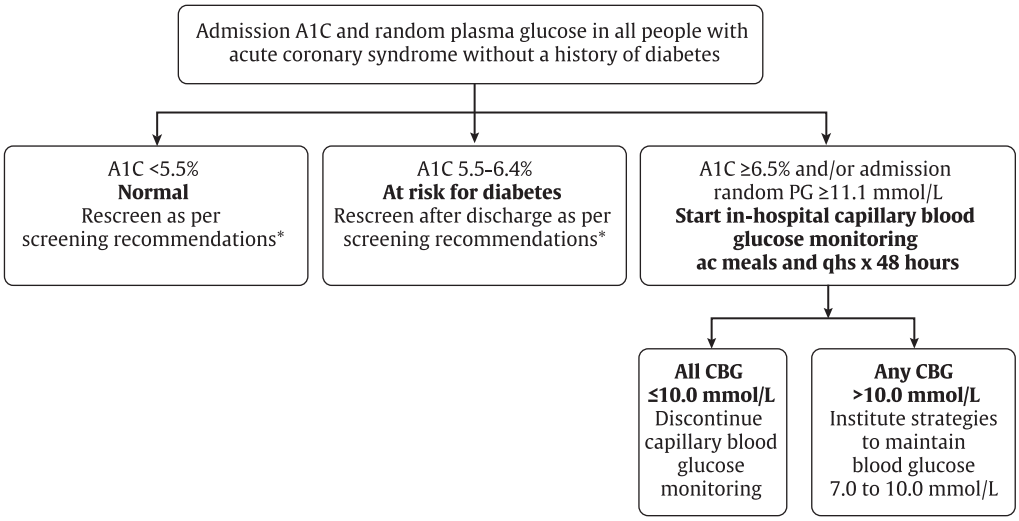

ACS, acute coronary syndrome; *BG*, blood glucose; *CBG*; capillary blood glucose; *CBGM*, capillary blood glucose monitoring; *PG*; plasma glucose.
*See Figure 1. Screening for Diabetes in Adults chapter, p.S16.

Figure 1. Screening for type 2 diabetes in people with ACS.

need of glycemic control will be detected with these simple tests that can be widely applied. In-hospital capillary blood glucose monitoring should be started in individuals without a history of diabetes with an admission A1C ≥6.5% or random plasma glucose (PG) >10.0 mmol/L. Individuals with an A1C between 5.5% to 6.4% should have repeat screening after discharge as per diabetes screening guidelines (see Screening for Diabetes in Adults chapter, p. S16 and Figure 1).

Management of ACS in People With Diabetes

Guidelines for the management of people with ACS have been developed by the American College of Cardiology/American Heart Association (22–24) and the European Society of Cardiology (25,26). In most situations, there are no clinical trials that specifically address management of people with diabetes and ACS; however, subgroup analyses in people with diabetes and ACS show either a similar or enhanced benefit from treatment compared to the overall group for: a) reperfusion with fibrinolysis (27) or primary angioplasty (28) for ST-segment elevation ACS; and b) an early invasive strategy (29) with the use of dual anti-platelet therapy with acetylsalicylic acid (ASA) and clopidogrel (30), glycoprotein IIb/IIIa inhibitors and the newer P2Y12 platelet inhibitors (prasugrel and ticagrelor) in people with non-ST segment elevation ACS at high risk of recurrent ischemic events (31).

A significant care gap exists for people with diabetes not receiving guideline-recommended treatment compared to people without diabetes (10–12,15,16). It is possible that the underutilization of recommended treatment is one factor contributing to the adverse outcome of the person with diabetes and ACS.

Anti-Platelet Therapy and ACS in People With Diabetes

Platelet aggregation plays a central role in the development of the occlusive thrombus responsible for acute coronary occlusion in people with ACS. People with diabetes have a pro-thrombotic state due to dysfunctional and hyperactive platelets, endothelial dysfunction, elevated coagulation factors and decreased fibrinolysis (32). Increased platelet activity is due to multiple metabolic and cellular factors associated with diabetes that include endothelial dysfunction, the impact of hyperglycemia and deficient insulin action (32).

Diabetes is associated with an increased incidence of recurrent atherothrombotic events (33), including stent thrombosis (34). Anti-platelet therapy has been shown to reduce atherothrombotic events in people with ACS, both during the acute phase and in the longer term. The beneficial effect of ASA has been shown in multiple clinical trials in patients with non–ST-segment elevation acute coronary syndrome (NSTE ACS) and ST-segment elevation MI (STEMI). The Antithrombotic Trialist's Collaboration meta-analysis (35) of anti-platelet therapy (mainly ASA) included 212,000 high-risk participants (with acute or previous vascular disease) and showed the incidence of vascular events to be reduced in both the overall population (16.8% to 12.8%; p<0.00001) and in the participants with diabetes (22.3% to 18.5%; p<0.002). Low-dose ASA (75 to 150 mg) was as effective as higher doses (>150 mg) with a lower incidence of bleeding complications. The Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes (CURRENT/OASIS 7) trial (36) also was unable to show any benefit from higher dose compared to low-dose (75 to 100 mg) ASA in people with and without diabetes. The use of low-dose ASA is recommended to minimize GI bleeding in people with and without diabetes (see Cardiovascular Protection in People with Diabetes chapter, p. S162).

Dual anti-platelet therapy with ASA and clopidogrel, administered from the time of presentation, has been the recommended standard of care for people with NSTE ACS. People with diabetes in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (30) had a similar benefit with clopidogrel vs. placebo (14.2% vs. 17.7%, RR 0.84, 95% CI 0.70–1.02) as the overall population (9.3% vs. 11.4%, RR 0.80, 95% CI 0.72–0.90). Despite dual-antiplatelet therapy with ASA and clopidogrel, recurrent atherothrombotic events continue to occur, especially in the person with diabetes. Clopidogrel is a relatively weak inhibitor of platelet aggregation with a wide variation of inhibition of in-vitro platelet aggregation. There is a higher incidence of events in people with residual platelet activity and people with diabetes have higher residual platelet activity despite ASA and clopidogrel treatment. Two more potent antiplatelet agents, prasugrel and ticagrelor, that are more effective and predictable inhibitors of platelet aggregation, have been shown to improve outcomes, especially in people with diabetes.

In the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel - Thrombolysis In Myocardial Infarction (TRITON-TIMI 38) trial, prasugrel administered at the time of coronary angioplasty in participants with ACS reduced recurrent ischemic events, including stent thrombosis, compared to participants receiving clopidogrel (37). In subjects with diabetes, prasugrel treatment was associated with greater platelet inhibition and fewer poor responders (38). Prasugrel resulted in an important net clinical benefit in people with diabetes (39) (14.6 vs. 19.2%, HR 0.74, p=0.001) due to a 30% reduction of the primary endpoint (cardiovascular [CV]) death, non-fatal MI or stroke over the 14.4 months of the study. In this subgroup with diabetes, there was no significant increase in major bleeding. There was no statistical interaction between the subgroups with and without diabetes, indicating that the enhanced absolute benefit was the result of higher event rates in people with diabetes.

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, the $P2Y_{12}$ receptor antagonist ticagrelor, when compared with clopidogrel and administered early after presentation in people with NSTE ACS or STEMI, reduced CV death, non-fatal MI and stroke (10.2% vs. 12.3%, HR 0.84, p=0.0001), as well as CV death (4.0% vs. 5.1%, HR 0.49, p=0.001) and stent thrombosis (2.2% vs. 2.9%, HR 0.75, p=0.02) with a modest increase in bleeding in people not undergoing coronary bypass surgery (40). In the diabetic cohort of the PLATO study, similar benefits were observed as in the overall group (41).

The availability of more potent and reliable anti-platelet agents for the management of people with ACS provides an opportunity to further reduce recurrent ACS and mortality. High-risk people with diabetes with either STEMI or NSTE ACS should be considered for treatment with either prasugrel (after the coronary disease anatomy has been defined) or ticagrelor.

Platelet aggregation is largely mediated by the glycoprotein (GP) IIb/IIIa receptor through its binding to fibrinogen. The GPIIb/IIIa receptor inhibitors abciximab, eptifibatide and tirofiban were shown to be effective for the management of ACS in people with diabetes in a meta-analysis of 6 clinical trials. GPIIb/IIIa inhibitors were shown to reduce 30-day mortality by 26% (4.6% vs. 2.6%, p=0.007) (31). In contrast, people without diabetes had no mortality benefit. Although these trials were performed in an era before dual anti-platelet therapy with ASA and clopidogrel was used, studies (42,43) indicate an additional benefit from a GPIIb/IIIa inhibitor for people with high-risk ACS, such as those with diabetes who are undergoing percutaneous coronary intervention (PCI). However, these benefits have not been observed when more potent oral anti-platelet agents, such as ticagrelor, are used (44).

More prolonged duration dual anti-platelet therapy with ASA and ticagrelor in people with ACS, administered for up to 3 years beyond the usual 1-year treatment, was shown in the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial to reduce the primary endpoint of non-fatal MI, stroke or CV death (placebo 9.04% ticagrelor 60 mg 7.77% (hazard ratio [HR] 0.84, 95% CI 0.74–0.95), ticagrelor 90 mg 7.85% (HR 0.85, 95% CI 0.75–0.96) (44). There was no advantage to receiving ticagrelor 90 mg twice daily rather than 60 mg twice daily, and major bleeding was slightly more at the higher dose (placebo 1.06%, ticagrelor 60 mg 2.3%, ticagrelor 90 mg 2.6%). Participants with diabetes receiving ticagrelor, had a similar relative risk reduction of the primary combined endpoint as the overall group (45). However, with a 50% higher event rate, those with diabetes had an 60% greater absolute benefit than the participants without diabetes (participants with diabetes: placebo 11.6%, ticagrelor 60 mg twice daily 10.0% [HR 0.83, 95% CI 0.69–1.00]; participants without diabetes: placebo 7.8%, ticagrelor 6.7% [HR 0.84, 95% CI 0.72–0.98]). The increased bleeding rates with ticagrelor were similar in the people with diabetes to those without diabetes. People at very high risk or recurrent ischemic events (such as people with extensive coronary artery disease [CAD] not completely revascularized, or recurrent ACS despite usual recommended treatment) and with a low or average bleeding risk, should be considered for prolonged (up to 3 years post-ACS) treatment with ticagrelor 60 mg twice daily.

Glycemic Control

Hyperglycemia during the first 24 to 48 hours after admission for ACS is associated with an increased early mortality, whether or not the person has diabetes (46,47). Furthermore, in-hospital mortality has a closer relationship to hyperglycemia than to diabetic status (48,49). Higher baseline blood glucose (BG) and a failure of BG to decrease are independent predictors of mortality (50). For people undergoing primary angioplasty, mortality increases when the plasma glucose (PG) is >10.0 mmol/L (47).

Although elevated mean BG level in the first 24 hours after onset of ACS is associated with adverse outcomes (51), evidence to support reducing BG levels (especially to levels close to the normal range) after ACS, remains inconclusive. The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study indicated that tight glycemic control with the use of intravenous insulin in the early hours after presentation, followed by multidose subcutaneous insulin treatment over the subsequent months, resulted in a 30% reduction in 1-year mortality (52–56). The DIGAMI 2 study failed to achieve the study goals, both in the number of participants recruited and in glycemic targets (52). However, despite these limitations, it did demonstrate that outcomes were closely related to glycemic control, however achieved. Studies have shown that glucose-insulin-potassium infusion in patients with AMI do not improve outcomes; however, these protocols often resulted in increased BG levels and, therefore, cannot be used as evidence for outcomes associated with glycemic control. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study of glucose and insulin in people with AMI, participants with a blood glucose maintained at <8.0 mmol/L had lower mortality than subjects with higher levels (57).

In conclusion, clinical trial data do not conclusively show that tight glycemic control early after an ACS improves long-term outcomes. Furthermore, the impact of hypoglycemia may negate any potential benefit. Glycemic control in the post MI patient should be consistent with the Diabetes Canada clinical practice guidelines recommendations for management of hyperglycemia in the hospitalized patient (see In-Hospital Management of Diabetes chapter, p. S115).

Revascularization

ACS practice guidelines promote the same treatment strategies in people with diabetes as for those without diabetes (58) . An early invasive strategy with revascularization when possible in non-ST elevation (NSTE) ACS provides a similar or greater reduction in death and MI (up to 5 years of follow up) in the subset of participants with diabetes compared to the overall population (27,59,60). An early invasive, rather than a selective invasive (conservative), strategy is recommended, in the absence of contraindications in people with diabetes and a NSTE ACS.

Trials comparing coronary artery bypass grafting (CABG) and PCI in people with diabetes with stable multivessel disease or ACS have provided consistent results in favour of CABG (61) with improved outcomes of death, MI and repeat revascularization, despite an excess of stroke in people undergoing CABG. These results are generally extrapolated to the higher-risk ACS population with diabetes with

NSTE-ACS and complex coronary anatomies. Therefore, CABG with the use of internal thoracic artery bypass should be the preferred revascularization modality over complex PCI in light of the consistent results in randomized trials with the provision that patient characteristics (such as frailty, cerebrovascular disease, among others) need to be considered. Percutaneous coronary interventions (with newer generation drug-eluting stents whenever possible) is acceptable for people with less extensive disease (i.e. single-vessel disease or 2-vessel disease without involvement of the left anterior descending (LAD) and those with Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score ≤22) (62).

For people with ST-elevation ACS, immediate reperfusion strategies with either fibrinolysis or primary PCI (PPCI) result in similar benefits for people with and without diabetes. The benefits of PPCI over fibrinolysis in people with diabetes are similar to those in the population without diabetes (Odds ratio [OR] mortality with primary PCI vs. fibrinolysis in people with diabetes 0.49 [95% CI 0.31–0.79]) (27). However, fibrinolysis should be administered when PPCI is not available, within acceptable timeframes. Ocular hemorrhage in people with diabetic retinopathy is extremely rare and should not limit the use of fibrinolysis when it is indicated (59).

RECOMMENDATIONS

1. In all people with ACS, a random BG and an A1C (if not done in the 3 months prior to admission) should be measured:
   a. For people with a history of diabetes, to identify individuals that would benefit from glycemic optimization [Grade D, Consensus]
   b. For people without a history of diabetes, to identify individuals at risk for ongoing dysglycemia [Grade D, Consensus]
      i. If the A1C is ≥6.5% and/or random BG is >11.0 mmol/L, in-hospital capillary blood glucose monitoring should be initiated [Grade D, Consensus]
      ii. If A1C is 5.5–6.4%, repeat screening for diabetes should be performed after discharge as per diabetes screening recommendations [Grade D, Consensus]) (see Figure 1. Screening for Diabetes in Adults chapter, p. S16).

2. In-hospital management of diabetes in ACS should include strategies to avoid both hyperglycemia and hypoglycemia:
   a. People with ACS and a random BG of >11.0 mmol/L on admission may be treated to achieve BG levels in the range of 7.0–10.0 mmol/L followed by strategies to achieve recommended BG targets long term [Grade C, Level 2 (52,55)]. Insulin therapy may be required to achieve these targets [Grade D, Consensus]
   b. An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia [Grade D, Consensus].

3. People with diabetes and ACS should receive the same treatments that are recommended for people with ACS without diabetes since they benefit equally [Grade D, Consensus].
   a. In people with diabetes and ACS undergoing PCI, antiplatelet therapy with prasugrel (if clopidogrel naïve, <75 years of age, weight >60 kg, and no history of stroke) [Grade A, Level 1 (37,39)] or ticagrelor [Grade B, Level 1 (40,41)], rather than clopidogrel, should be used to further reduce recurrent ischemic events. People with diabetes and non-STE ACS and higher risk features destined for a selective invasive strategy should receive ticagrelor, rather than clopidogrel [Grade B, Level 2 (40,41)]
   b. In people with diabetes and ACS, at very high risk of recurrent ischemic events and at average or low bleeding risk, prolonged (up to 3 years post ACS) treatment with ticagrelor 60 mg twice daily should be considered [Grade B, Level 2 (45)]
   c. In people with diabetes and non-STE ACS and high risk features, an early invasive approach, rather than a selective invasive approach to revascularization, should be used to reduce recurrent coronary events, unless contraindicated [Grade B, Level 2 (29)]
   d. For people with diabetes with NSTE-ACS and complex coronary anatomy, CABG should be considered rather than complex PCI [Grade A, Level 1 (62)]
   e. In people with diabetes and STE-ACS, the selection of the reperfusion modality (PPCI vs. fibrinolysis) should not differ from people with STE-ACS without diabetes; the presence of retinopathy should not be a contraindication to fibrinolysis [Grade B, Level 2 (59)].

Abbreviations:
A1C, glycated hemoglobin; *ACS*, acute coronary syndrome; *AMI*, acute myocardial infarction; *ASA*, acetylsalicylic acid; *BG*, blood glucose; *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *CV*, cardiovascular; *FPG*, fasting plasma glucose; *HR*, hazard ratio; *IGT*, impaired glucose tolerance; *LV*, left ventricular; *MI*, myocardial infarction; *NSTE*, non-ST-elevation; *OGTT*, oral glucose tolerance test; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; *PG*, plasma glucose; *PPCI*, primary percutaneous coronary intervention; *STEMI*, ST-segment elevation myocardial infarction.

Other Relevant Guidelines

In-Hospital Management of Diabetes, p. S115.

Author Disclosures

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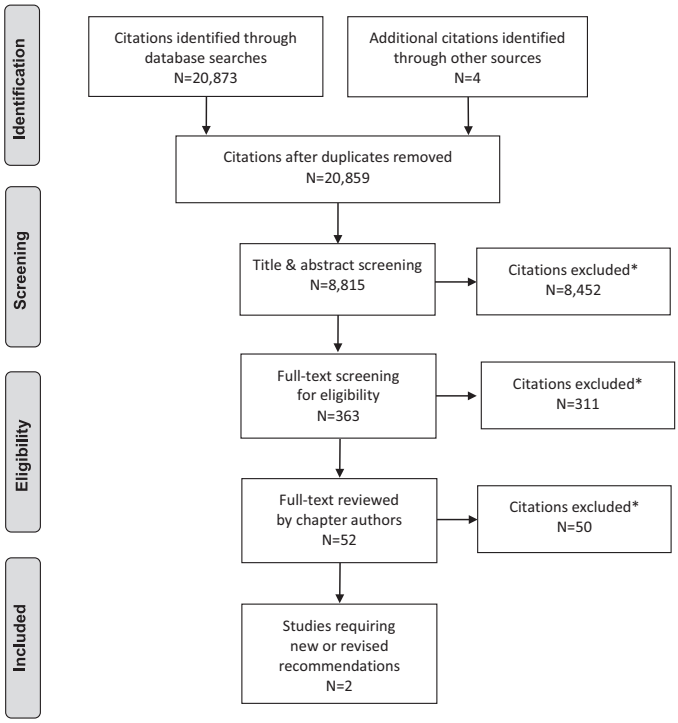
Literature Review Flow Diagram for Chapter 27: Management of Acute Coronary Syndromes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (63).

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2018 Clinical Practice Guidelines

Treatment of Diabetes in People With Heart Failure

Diabetes Canada Clinical Practice Guidelines Expert Committee

Kim A. Connelly MBBS, PhD, FCCS, Richard E. Gilbert MBBS, PhD, Peter Liu MD, FRCPC, FACC

KEY MESSAGES

- Heart failure is still under-recognized and misdiagnosed. This has significant clinical implications as the prognosis of untreated or undertreated heart failure is poor, and yet very effective proven therapies are widely available to most.
- Diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy that may manifest in the setting of normal or reduced left ventricular ejection fraction. The incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without and, when present, occurs at an earlier age.
- Even though heart failure in people with diabetes should be treated similarly to heart failure in those without diabetes, they are less likely to receive appropriate therapies. The presence of diabetes should not affect the decision for treatment of heart failure.
- Comorbidities, such as renal dysfunction and propensity for hyperkalemia, are more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy but not therapeutic targets.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Heart failure is a type of heart disease in which the heart no longer pumps sufficient blood to meet the body's needs. Diabetes is a risk factor for heart failure.
- Symptoms of heart failure include shortness of breath, persistent coughing, fatigue, chest pain, weight gain or swelling of the feet, ankles and legs.
- A number of effective drug treatments are available to keep heart failure in check. Your health-care provider will discuss these with you.
- Certain glucose-lowering medications have the potential to worsen or help heart failure. If you have heart failure, this will influence which glucose-lowering medications your health-care provider selects for you.

Introduction

Type 2 diabetes often occurs in association with other cardiovascular (CV) risk factors, such as hypertension, dyslipidemia, smoking and obesity, which, together, are strongly associated with atherosclerosis, ischemic heart disease and left ventricular (LV) dysfunction (1). LV dysfunction can be clinically silent or associated with the typical clinical signs and symptoms of heart failure (e.g. peripheral edema, shortness of breath, fatigue), although the elderly may have atypical symptoms (2). These symptoms need to be differentiated from other conditions that may have similar presentations, such as chronic obstructive pulmonary disease, pneumonia, anemia, varicose veins, depression, etc.

Heart Failure in People with Diabetes

The diagnosis of heart failure is made by association of typical clinical signs and symptoms with objective evidence, such as that obtained from a chest x-ray, an echocardiogram or plasma natriuretic peptide testing (brain natriuretic peptide [BNP] and prohormone of BNP [NT-pro-BNP]) (2). Documentation of systolic and diastolic myocardial function is recommended at the time of diagnosis of heart failure or with any significant change in clinical stability. Heart failure can occur over the entire range of left ventricular ejection fractions (LVEF), from <10% to >60%. The measurement of plasma BNP and NT-pro-BNP, which are acutely released by ventricular myocytes when the myocardium is stretched due to increased filling pressures, may help make an accurate diagnosis where clinical uncertainty exists (3). However, the practicing health-care provider may still under-recognize and misdiagnose heart failure. This has significant clinical implications as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available. Because of this, many studies have explored the clinical utility of screening people with diabetes for the presence of reduced LV function with BNP/NT-pro- BNP testing. The results to date are mixed, with no clear consensus to institute this strategy. A recent analysis of the Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) study assessed a number of biomarkers, including high sensitive C-reactive protein (hs-CRP), highly sensitive troponin T (hs-TnT) assay and interleukin 6. In a cohort of 3,098 participants in the ADVANCE study who underwent a nested case-cohort study, only NT-pro-BNP strongly and consistently improved the prediction of heart failure (4).

Diabetes is associated with increased prevalence of heart failure, both systolic (commonly defined as LVEF <40% or heart failure with a reduced ejection fraction) and diastolic (commonly defined as LVEF >50%, but also referred to as preserved systolic function or heart failure with preserved EF). However, the overlap between heart failure with preserved EF and reduced EF is considerable, and many people have a combination of systolic and diastolic dysfunction, although one is often reported to be predominant. Current tests, such as echocardiography, do usually fully characterize all aspects of systolic and diastolic dysfunction in individuals.

It is recognized that diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic

Conflict of interest statements can be found on page S199.

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cardiomyopathy (5). Epidemiological studies have shown that the incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without diabetes (6,7). Additionally, studies have shown the occurrence of asymptomatic abnormalities of ventricular systolic and diastolic function, independently from ischemic heart disease or systemic hypertension. While an increase in glycated hemoglobin (A1C) among individuals with diabetes is a recognized risk factor for heart failure (8–12), no prospective study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (13). Albuminuria is also an independent risk factor for heart failure, especially in people with diabetes. In individuals with and without diabetes, an increasing urinary albumin to creatinine ratio (ACR) is associated with a stepwise increase (2- to 4-fold) in the risk of heart failure development (10,14). Blockade of the renin angiotensin aldosterone system (RAAS) has been shown in large clinical trials of participants with cardiovascular disease (CVD) or diabetes to lower the risk of new-onset heart failure (15–17).

Treatment of Individuals with Both Diabetes and Heart Failure

In nearly every clinical trial involving people with heart failure, diabetes is present in over one-third of subjects. In the large landmark clinical trials of heart failure, subgroup analysis of populations with diabetes has shown that, despite their increased risk of morbidity and mortality, they derive greater absolute benefit from efficacious therapies as compared to people without diabetes (17–19). This was again demonstrated in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial in which 8,442 participants with class II, III or IV heart failure and an EF of ≤40% were randomized to receive either LCZ696 (sacubitril/valsartan at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to routine heart failure therapy. The primary outcome was a composite of death from CV causes or hospitalization for heart failure. LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure ($p<0.001$) (20). An analysis of 4,013 participants in the trial who had a diagnosis of diabetes based on A1C or prior history demonstrated that LCZ696 remained similarly efficacious, regardless of glycemic status (21). A similar finding was observed with the Systolic Heart failure treatment with the I_f inhibitor ivabradine (SHIFT) trial (22), a randomized trial of ivabradine vs. placebo in 6,505 participants with sinus rhythm, systolic heart failure, ejection fraction <35% and a resting heart rate >70 bpm. There were 1,979 participants with diabetes who achieved the primary composite endpoint of hospitalization for worsening heart failure or CV death more frequently than those without diabetes (Hazard Ratio [HR] 1.18, 95% Confidence Interval [CI] 1.07–1.31, $p=0.001$). Serious adverse events were not different between the ivabradine or placebo group, regardless of diabetes status. Overall, ivabradine is effective in this patient group irrespective of diabetic status. As such, heart failure in people with diabetes should be treated similarly to those without diabetes (23).

Therapeutic Considerations for Individuals with Both Diabetes and Heart Failure

People with diabetes are at increased risk for development of hyperkalemia and worsening renal dysfunction in the setting of RAAS blocking agents (24–29). Clinicians should be aware of this potential complication, especially in view of current guidelines advocating the expanded use of combined RAAS blockade in people with mild-to-moderate heart failure and low EF.

Three beta blockers have been shown to reduce morbidity and mortality for people with heart failure, reduced EF and diabetes: carvedilol, bisoprolol and metoprolol succinate. While overall glycemic control generally improves as heart failure is treated with evidence-based therapies, (30–32), carvedilol, in comparison to other beta blockers, has been shown to specifically improve glycemic control (19,33). For this reason, some clinicians prefer carvedilol as the beta blocker of choice in people with diabetes and heart failure. While there is a theoretical concern for the occurrence of severe hypoglycemia without awareness associated with the use of non-selective beta blockers, this has not been reported in clinical trials.

Numerous registries and reports indicate that persons with diabetes are less likely than those without diabetes to receive efficacious and evidence-based therapies for systolic heart failure. Perhaps this is due, in part, to the increased incidence of side effects and/or intolerance to RAAS blockade and the increased prevalence of renal disease in people with diabetes. However, even when controlled for these conditions, the differences persist. This is particularly concerning considering the increased absolute benefit the agents confer to people with heart failure and diabetes in comparison to unselected heart failure populations. As such, health-care prescribers must be diligent in providing these therapies.

Antihyperglycemic Agents and Heart Failure

Despite substantial understanding of the impact of antihyperglycemic therapy upon glucose control and microvascular disease, the heart failure specific response to intensive glycemic control and the various antihyperglycemic agents (discussed below) remains poorly understood (34).

Metformin

Metformin is an effective noninsulin antihyperglycemic agent but, based on isolated case reports and a biochemical rationale for a risk of lactic acidosis, it is approved for use under a warning in the setting of several conditions, including heart failure. Meta-analyses have evaluated the occurrence of lactic acidosis with the use of metformin (over 70,000 patient-years) or other antihyperglycemic agents (over 55,000 patient-years) and they have consistently shown no increase in lactic acidosis in the metformin group (35,36). In fact, CV outcomes in people with heart failure taking metformin were better than in those taking other conventional antihyperglycemic agents (37). The current evidence suggests that people with heart failure fare at least as well, if not better, with metformin than with other antihyperglycemic agents if they have only mild-to-moderate renal dysfunction (eGFR >30 mL/min) (37). As such, metformin should still be considered as first-line therapy in people with diabetes with heart failure with mild-to-moderate renal dysfunction (38).

Thiazolidinediones

Thiazolidinediones (TZDs) are known to cause fluid retention, although this is generally mild. Recent studies suggest that this is not a direct toxic effect on the myocardium. The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) study of pioglitazone in individuals at risk of cardiac ischemic events showed that TZDs were associated with fewer cardiac ischemic events, but at the cost of an increase in heart failure hospitalizations (2% absolute excess over 2.8 years, or <1% per year) (39). Similarly, The Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study demonstrated a small excess of new-onset heart failure (0.4% absolute excess).

The RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) was a multicentre,

open-label study that randomized 4,447 people with type 2 diabetes on metformin or sulfonylurea monotherapy to add-on rosiglitazone (n=2,220) or to a combination of metformin and sulfonylurea (n=2,227) (40). In the rosiglitazone group, the risk of heart failure death or hospitalization was doubled (HR 2.10, 95% CI 1.35–3.27): the excess heart failure event rate was 2.6 (95% CI 1.1–4.1) per 1,000 person-years. These findings confirm the increased risk of heart failure events in people treated with rosiglitazone. Since January 2012, Health Canada has advised that, "Avandia is contraindicated in patients with New York Heart Association (NYHA) Class I, II, III or IV heart failure." Further, under serious warnings and precautions, it states that "Avandia, like other thiazolidenediones, can cause fluid retention and congestive heart failure". A meta-analysis has not confirmed any difference in the risk of congestive heart failure (CHF) between rosiglitazone and pioglitazone (41,42).

CV outcome trials to assess for non-inferiority (CV safety) or superiority of new antihyperglycemic therapies have been undertaken in different diabetic populations with pre-specified secondary heart failure endpoints reported as mandated by the Food and Drug Administration (FDA) in December 2008. These CV safety studies include incretin agents (DPP-4 inhibitors and GLP-1 receptor agonists), as well as SGLT2 inhibitors. The mechanism of action and antihyperglycemic effects of these agents are detailed in the Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88. The information detailed below pertains directly to heart failure outcomes in people with diabetes. Of relevance, these trials were not heart failure trials per se and included only a small proportion of people with heart failure and reduced EF, hence the findings are limited in their generalizability to a broader heart failure population.

DPP-4 inhibitors

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial (SAVOR-TIMI 53) (43), the sitagliptin cardiovascular outcome study (TECOS) (44) and the Examination of Cardiovascular Outcomes with Alogliptin vs. Standard of Care (EXAMINE) (45), the endpoint of noninferiority, but not superiority was reached, suggesting these drugs have a neutral CV profile. There was an unexpected finding of increased hospitalization for heart failure noted with saxagliptin that was not seen in CV trials with the other DPP-4 inhibitors (46). Chronic kidney disease, elevated natriuretic peptide levels and previous heart failure were associated with an increased risk for heart failure hospitalization in SAVOR-TIMI 53. A secondary analysis of the EXAMINE trial did not demonstrate excess risk for heart failure hospitalization (46). Recent post-marketing, large registries and meta-analyses demonstrate overall neutrality for the class as a whole regarding heart failure (47). However, as a result of an excess risk demonstrated in the SAVOR-TIMI 53 trial, both the FDA and Health Canada have issued a warning for saxagliptin and heart failure, and the FDA has issued a similar warning for alogliptin. Specifically, the recommendation from the FDA for saxagliptin and alogliptin reads: "Healthcare professionals should consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control." In Canada, the product monograph for saxagliptin states, under warnings and precautions: "Caution is warranted if ONGLYZA (saxagliptin) is used in patients with history of congestive heart failure (especially in those patients who also have renal impairment and/or history of MI)" (48).

GLP-1 receptor agonists

Three large trials investigating GLP-1 receptor agonists were recently reported. The primary outcomes are reported in the Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter (see S88). In each trial, heart failure hospitalization was a pre-specified endpoint. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (49), the Evaluation of CV outcomes in patients with type 2 diabetes after ACS using Lixisenatide (ELIXA) trial (50), and the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN)-6 trial (51) were recently reported and demonstrated no excessive risk for heart failure hospitalization. Treatment with liraglutide in the LEADER trial was associated with a non-significant 13% reduction in heart failure hospitalization (HR 0.87, 95% CI 0.73–1.05, p=0.14), lixisenatide treatment in the ELIXA trial demonstrated a HR of 0.96, 95% CI 0.75–1.23, p=0.63) and semaglutide therapy in the SUSTAIN-6 trial demonstrated a HR of 1.11, 95% CI 0.77–1.6), with a nonsignificant p value of 0.57. Heart failure was present at baseline in ~17.8%, ~22.4% and ~23.6% of participants in LEADER, ELIXA and SUSTAIN-6, respectively. Finally, the impact of liraglutide on people with reduced EF was studied by Margulies et al. in the Functional impact of GLP-1 for Heart failure treatment (FIGHT) study. Three hundred participants (59% with diabetes) with a mean LVEF of 25% who were on evidence-based heart failure therapy were randomized to placebo or liraglutide. The primary endpoint was time to death, time to rehospitalization for heart failure and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days. There was no difference in the primary endpoint (HR 1.10, 95% CI 0.57–2.14, p=0.78). However, in people with diabetes, the HR was 1.54 (95% CI 0.97–2.46, p=0.07) for the endpoint of death or hospitalization for heart failure. These findings suggest no benefit from liraglutide in that clinical situation (52).

SGLT2 inhibitors

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial (53) demonstrated CV superiority with reduction in CV death, hospitalization for heart failure and all-cause mortality compared to placebo. While only 10.5% of participants enrolled in this study had pre-existing heart failure, there was a 35% reduction in heart failure hospitalization (p=0.0017, 95% CI 0.50–0.85). Furthermore, empagliflozin reduced the risk of heart failure hospitalization by a similar degree regardless of whether the participants had a prior history of heart failure or not. The mechanisms of benefit remains speculative. The other SGLT2 inhibitor trial with canagliflozin, CANagliflozin cardioVascular Assessment Study (CANVAS) trial (54) was recently reported. This met the prespecified noninferiority MACE endpoint and demonstrated superiority over standard care (p=0.02, HR 0.86, 95% CI 0.75–0.97). However, based on hierarchical sequential testing, the trial did not demonstrate a reduction in all-cause mortality and, therefore, all other prespecified endpoints were considered exploratory. Hospitalization for heart failure was reduced (HR 0.67, 95% CI 0.52–0.87), although not considered statistically significant. The Dapagliflozin (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) will report in November 2018 (ClinicalTrials.gov Identifier: NCT01730534).

Importantly, heart failure studies will soon commence utilizing SGLT2 inhibitors irrespective of glycemia status. The effect of dapagliflozin on time to first worsening heart failure event or CV death in people with heart failure and reduced EF, irrespective of glycemic status, has begun recruiting (ClinicalTrials.gov Identifier: NCT03036124) (55) and 2 trials are underway in patients with heart failure with a preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) using empagliflozin (ClinicalTrials.gov Identifier: NCT03057977 and NCT03057951) (56,57).

A detailed discussion of the rationale and evidence for the treatment approach to people with heart failure is available in the Canadian Cardiovascular Society consensus recommendations (http://www.ccsguidelineprograms.ca) (23).

RECOMMENDATIONS

1. Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society Heart Failure recommendations (http://www.onlinecjc.ca/article/S0828-282X(17)30973-X/pdf) [Grade D, Consensus (23)].

2. Unless contraindicated, metformin may be used in people with type 2 diabetes and heart failure [Grade C, Level 3 (18,38)]. Metformin should be temporarily withheld if renal function acutely worsens, and should be discontinued if renal function significantly and chronically worsens [Grade D, Consensus].

3. For people with NYHA class I-IV, exposure to TZDs should be avoided [Grade A, Level 1 (41)].

4. Beta blockers should be prescribed when indicated for heart failure with reduced ejection fraction, as they provide similar benefits in people with or without diabetes [Grade B, Level 2 (19,33)].

5. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m^2, an SGLT2 inhibitor with demonstrated heart failure hospitalization reduction may be added to reduce the risk of heart failure hospitalization [Grade B, Level 2 (53) for empagliflozin; Grade C, Level 2 (54) for canagliflozin].

6. In adults with diabetes and heart failure with an eGFR <60 mL/min/1.73m^2 and/or if combined RAAS blockade is employed:
   a. Starting doses of ACE inhibitors or ARBs should be halved [Grade D, Consensus]
   b. Serum electrolytes and creatinine, BP and body weight, as well as heart failure symptoms and signs, should be monitored within 7–10 days of any initiation or titration of therapy [Grade D, Consensus]
   c. Dose-up titration should be more gradual (with monitoring of BP, serum potassium and creatinine) [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *ACE*, angiotensin-converting enzyme; *ACR*; albumin to creatinine ratio; *ARB*, angiotensin receptor blocker; *BNP*, brain natriuretic peptide; *BP*, blood pressure; *CI*, confidence interval; *CV*, cardiovascular; *EF*, ejection fraction; *eGFR*; estimated glomerular filtration rate; *FDA*; Food and Drug Administration; *HR*, hazard ratio; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *NT-pro-BNP*, pro-hormone of BNP; *NYHA*, New York Heart Association; *RAAS*, renin angiotensin aldosterone system; *TZD*, thiazolidinedione.

Other Relevant Guidelines

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Chronic Kidney Disease in Diabetes, p. S201

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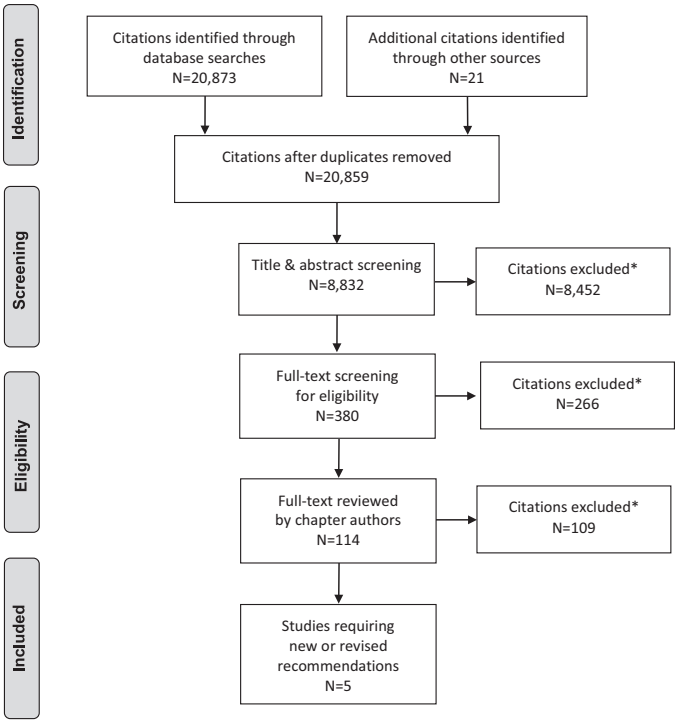
Literature Review Flow Diagram for Chapter 28: Treatment of Diabetes in People with Heart Failure



*Excluded based on: population, intervention/exposure, comparator/control or study design

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (58).

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2018 Clinical Practice Guidelines

Chronic Kidney Disease in Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

Philip McFarlane MD, PhD, FRCPC, David Cherney MD, PhD, FRCPC, Richard E. Gilbert MBBS, PhD, FACP, FRACP, FRCPC, Peter Senior MBBS, PhD, FRCP

KEY MESSAGES

- Identification of chronic kidney disease in people with diabetes requires screening for proteinuria, as well as an assessment of serum creatinine converted into an estimated glomerular function rate (eGFR).
- All individuals with chronic kidney disease should be considered at high risk for cardiovascular events and should be treated to reduce these risks.
- The development and progression of renal damage in diabetes can be reduced and slowed through intensive glycemic control and optimization of blood pressure. Progression of chronic kidney disease in diabetes can also be slowed through the use of medications that disrupt the renin angiotensin aldosterone system.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- The earlier that the signs and symptoms of chronic kidney disease in diabetes are detected, the better, as it will reduce the chance of progression to advanced kidney disease and the need for dialysis or transplant.
- You should have your blood and urine tested annually for early signs of chronic kidney disease in diabetes.
- If you are found to have signs of chronic kidney disease, your health-care provider may recommend lifestyle or medication changes to help delay more damage to your kidneys.

PRACTICAL TIPS

Management of Potassium and Creatinine During the Use of Angiotensin Converting Enzyme (ACE) inhibitor or Angiotensin II Receptor Blocker (ARB) or Direct Renin Inhibitor (DRI) Therapy

- Check serum potassium and creatinine at baseline and within 1 to 2 weeks of initiation or titration of therapy AND during times of acute illness.
- If potassium becomes elevated or creatinine increases by more than 30% from baseline, therapy should be reviewed and serum creatinine and potassium levels should be rechecked.
- Mild-to-moderate stable hyperkalemia:
  - Counsel on a low-potassium diet.
  - If persistent, non-potassium-sparing diuretics and/or oral sodium bicarbonate (in those with a metabolic acidosis) should be considered.
  - Consider temporarily reducing or holding RAAS blockade (i.e. ACE inhibitor, ARB or DRI).
- Severe hyperkalemia:
  - In addition to emergency management strategies, RAAS blockade should be held or discontinued.

Introduction

Diseases of the kidney are a common finding in people with diabetes, with up to one-half demonstrating signs of renal damage in their lifetime (1–3). Diabetes is the leading cause of kidney disease in Canada (4). Kidney disease can be a devastating complication, as it is associated with significant reductions in both length and quality of life (5,6). A variety of forms of chronic kidney disease (CKD) in diabetes can be seen, including diabetic nephropathy, ischemic nephropathy related to vascular disease, hypertensive nephrosclerosis, as well as other renal diseases that are unrelated to diabetes (7,8) (Figure 1). This chapter discusses how to screen for and diagnose CKD in people with diabetes, how to slow its progression, and the impact of CKD on other aspects of diabetes management.

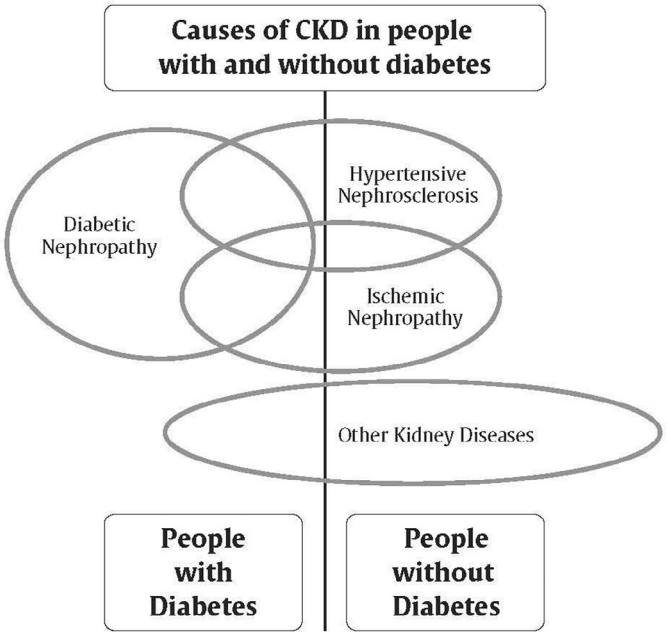

Figure 1. Causes of CKD in people with and without diabetes. *CKD*, chronic kidney disease.

Conflict of interest statements can be found on page S207.

https://doi.org/10.1016/j.jcjd.2017.11.004

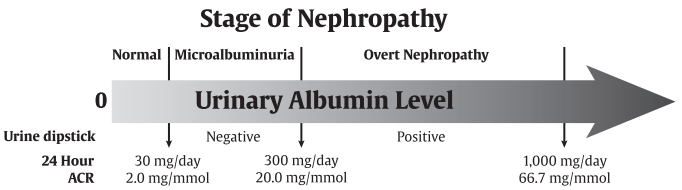

Figure 2. Level of urinary albumin by various test methods and stage of CKD in diabetes.
ACR, albumin to creatinine ratio; *CKD*, chronic kidney disease.

Diabetic Nephropathy

The classical description of diabetic nephropathy is a slow and progressive increase in albuminuria, followed later in the disease by a decrease in estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, which can, eventually, lead to end stage renal disease (ESRD) (1,9,10) (Figure 2). Key risk factors include long duration of diabetes; non-optimal glycemic, blood pressure and plasma lipid control; obesity (11); and cigarette smoking(12). Many of these risk factors are modifiable.

The earliest stage of diabetic nephropathy is hyperfiltration, where the glomerular filtration rate (GFR) is significantly higher than normal. Identification of hyperfiltration is not clinically useful, as it is difficult to determine from routine testing and is not present in all people with early diabetic nephropathy. Persistent albuminuria is considered the earliest clinical sign of diabetic nephropathy. Initially, small amounts of albumin are leaked, below the detection threshold of a urine dipstick. This stage is referred to as "microalbuminuria". Over time, albuminuria can worsen so that the urinary albumin excretion is sufficiently high to be detectable by a urine dipstick, a stage known as "overt nephropathy" (Table 1). The rate of progression from normoalbuminuria to microalbuminuria, then to overt kidney disease, is usually slow, typically taking five years or longer to progress through each stage (13,14). During the early stages of diabetic nephropathy, the rate of loss of renal function is relatively slow (a decrease in eGFR of 1 to 2 mL/min/1.73 m^2/year), and not impressively higher than what is seen in the general population (0.5 to 1.0 mL/min/1.73 m^2/year) (15). However, late in the overt kidney disease phase, the rate of decline of renal function can accelerate (5 to 10 mL/min/1.73 m^2/year). Thus, significant renal dysfunction is not usually seen until late in the course of diabetic nephropathy (16).

It is important to note that the rate of progression can vary between individuals, and that the clinical markers of the disease (i.e. eGFR, urinary albumin levels) do not always correlate well with the severity of renal disease seen on biopsy (17). Additionally, intensive glycemic control, optimization of blood pressure (BP), and the use of renal protective drugs, can slow or stop progression of diabetic nephropathy.

Other Kidney Diseases in People with Diabetes

Diabetic nephropathy is a major cause of CKD in diabetes; however, people with diabetes can also get CKD from other causes, including hypertensive nephrosclerosis or ischemic nephropathy from atherosclerotic changes to small or large renal arteries. In addition, there can be significant overlap (Figure 1). Ischemic nephropathy is characterized by a reduced GFR, usually with minimal or no increase in albuminuria. Kidney biopsy series in people with type 2 diabetes have found that non-diabetic glomerular disease, particularly ischemic kidney disease, is as common as CKD in diabetes in people with diabetes (7). Clinical studies have suggested that one-quarter to one-half of people with diabetes and significant kidney function impairment do not have albuminuria (18–20). These studies suggest that testing for albuminuria may be insufficient in identifying all people with diabetes who have renal disease. In addition to measurements of urinary albumin excretion, estimations of the level of kidney function and urinalyses are required to identify people with kidney disease other than diabetic nephropathy.

In most cases, the risk of ESRD in diabetes does not appear to matter whether the renal diagnosis is one of diabetic nephropathy or an alternative diagnosis, and the management is the same (21). However, Table 2 lists some concerning clinical and laboratory features that would lead to suspicion of a kidney disease unrelated to diabetes and require additional testing or referral, and possible renal biopsy (22–25).

Screening for Chronic Kidney Disease in People with Diabetes

Screening for CKD in people with diabetes involves an assessment of urinary albumin excretion and a measurement of the overall level of kidney function through an eGFR. Persistent abnormalities (lasting >3 months) of either urinary albumin excretion or eGFR, or significant urinalysis abnormalities lead to the diagnosis of CKD in people with diabetes. People with type 1 diabetes are not expected to have kidney disease at the time of onset of diabetes, so screening can be delayed until the duration of diabetes exceeds 5 years. Significant renal disease can be present at the time of diagnosis of type 2 diabetes (26,27), so screening should be initiated immediately at the time of diagnosis in this group.

Screening for Albuminuria

When screening for albuminuria, the test of choice is the random urine albumin to creatinine ratio (urine ACR). The 24-hour urine collection for protein/albumin remains the gold standard; however, it is cumbersome to implement on a large scale, inconvenient for people, and is often performed incorrectly (28–32). The random urine for albumin is insufficient, as the urinary albumin concentration can

Table 1
Stages of diabetic nephropathy by level of urinary albumin level

Stages of Diabetic Nephropathy by Level of Urinary Albumin Level			
Stage of nephropathy	**Urine dipstick for protein**	**Urine ACR (mg/mmol)**	**24-hour urine collection for albumin**
Normal	Negative	<2	<30 mg/day
Microalbuminuria	Negative	2-20	30-300 mg/day
Overt nephropathy	Positive	>20 >67	>300 mg/day >1,000 mg/day
Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 4).			

ACR, albumin to creatinine ratio.

Table 2
Clinical and laboratory factors favouring the diagnosis of classical diabetic kidney disease or an alternative renal diagnosis

Factors Favouring Classical Diabetic Nephropathy vs. Alternate Diagnoses	
Favours Diabetic Nephropathy	**Favours Alternate Renal Diagnosis**
Persistent albuminuria	Extreme proteinuria (>6 g/d)
Bland urine sediment	Persistent hematuria (micro- or macroscopic) or active urinary sediment
Slow progression of disease	Rapidly falling eGFR
Low eGFR associated with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes present	Other complications of diabetes not present or relatively not as severe
Known duration of DM >5 years	Known duration of diabetes <5 years
	Family history or nondiabetic renal disease (e.g. polycystic kidney disease)
	Signs or symptoms of systemic disease

eGFR, estimated glomerular filtration rate.

Table 3
Conditions that can cause transient albuminuria. The presence of such conditions should lead to a delay in screening for CKD

Potential Causes for Transient Albuminuria
Recent major exercise
Urinary tract infection
Febrile illness
Decompensated congestive heart failure
Menstruation
Acute severe elevation in blood glucose
Acute severe elevation in blood pressure

vary due to urine concentration (29). A random urine ACR predicts 24-hour urinary albumin excretion sufficiently well, and is the test of choice for screening for albuminuria (28,30–32). There is substantial day-to-day variability in albuminuria. In addition, transient and benign increases in albuminuria can be provoked by a number of factors (33–37) (Table 3). When such conditions are present, screening for kidney disease should be delayed to avoid positive results that are not caused by renal damage. Furthermore, diagnosing a person as having albuminuria requires the elevated urinary albumin level to be persistent. At least 2 out of 3 urine samples exhibiting elevations in urinary albumin levels over 3 months are required before it is considered to be abnormal (Figure 3).

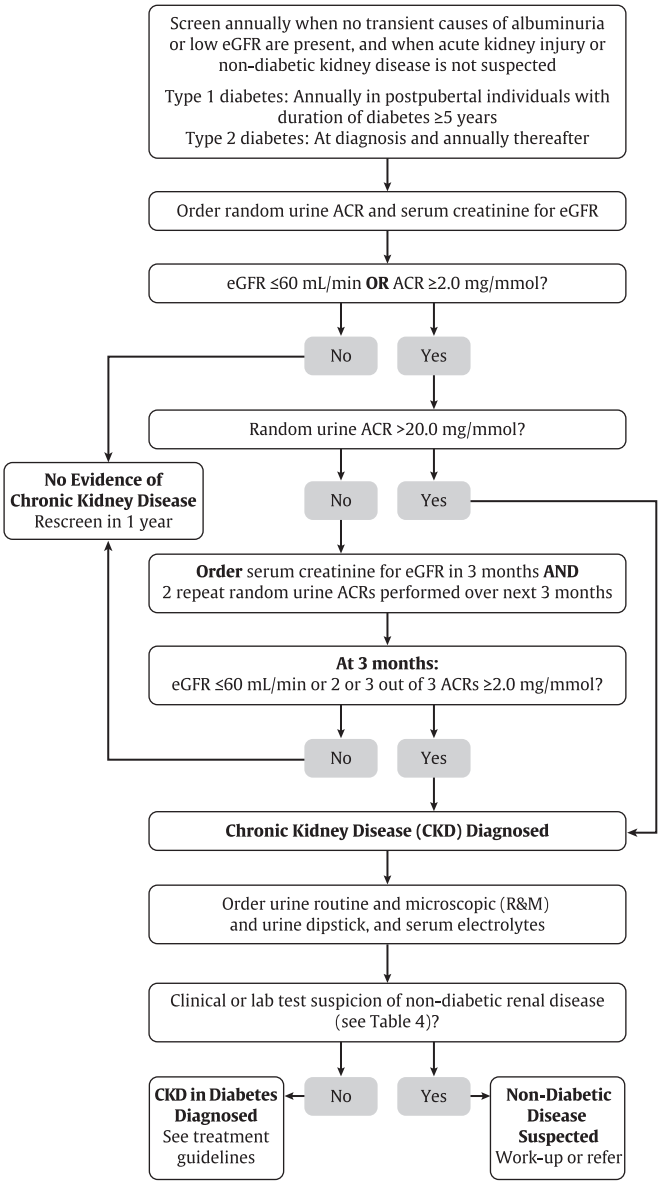

Figure 3. A flowchart for screening for CKD in people with diabetes.
ACR, albumin to creatinine ratio; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate.

Estimation of Glomerular Filtration Rate

The serum creatinine is the most common measurement of kidney function, however, it can inaccurately reflect renal function in many scenarios, particularly in extremes of patient age or size (38,39). Indeed, in people with diabetes, the GFR usually will be less than half of normal before the serum creatinine exceeds the lab normal range (40). As mentioned, measuring renal function using the 24-hour urine collection is cumbersome and can be difficult to perform accurately, so methods have been developed to estimate the glomerular filtration by combining the patient's serum creatinine with factors, such as age, weight and gender. The eGFR (estimated glomerular filtration rate) can be calculated using either the four-variable Modification of Diet in Renal Disease (MDRD) equation or the newer Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (41,42). These equations require knowledge of the person's age, sex, serum creatinine and race and is automatically computed and reported by many labs whenever a serum creatinine is ordered. Both equations perform well when the GFR is <60 ml/min/1.73 m^2 (43), but as the CKD-EPI is more accurate at higher levels of renal function (42), most medical laboratories across Canada now use this formula. The eGFR is generally a better estimate of glomerular filtration than the serum creatinine value alone, but is less accurate at extremes of age and size. A 24-hour urine for creatinine clearance can be used in individuals where there are concerns regarding the accuracy of the eGFR. Kidney diseases of all forms can be staged based on the degree of impairment of eGFR (Table 4).

Table 4
Stages of CKD of all types

Stages of CKD of all types		
Stage	**Qualitative Description**	**GFR (mL/min/1.73 m²)**
1	Kidney damage – normal GFR	> 90*
2	Kidney damage – mild ↓ GFR	60-89*
3a	Moderate ↓ GFR	45-59
3b	Moderate ↓ GFR	30-44
4	Severe ↓ GFR	15-29
5	End-stage renal disease	<15

*A GFR >60 mL/min/1.73 m² in isolation is not CKD, unless other evidence of kidney damage is present

CKD, chronic kidney disease; *GFR*, glomerular filtration rate

The eGFR is useful for assessing chronic changes in renal function but should not be used in situations where kidney function is changing rapidly. A rapid drop in renal function is referred to as an acute kidney injury (AKI). An AKI can occur in association with almost any acute systemic illness but, in particular, with conditions leading to hypotension or intravascular volume contraction. When such conditions are present, assessment of the level of kidney function may be clinically necessary, but should not be used to assess the stage of CKD. Because renal function can be transiently depressed, a persistent reduction in eGFR is required before it is considered to indicate the presence of CKD.

Other Clinical Features and Urinary Abnormalities—When to Consider Additional Testing or Referral

Urinalysis findings of red or white blood cell casts or heme granular casts suggest a renal diagnosis other than diabetic kidney disease. Although persistent microscopic hematuria can occur in people with diabetic nephropathy, its presence should lead to the consideration of other urologic or nephrologic conditions. Table 2 lists other clinical clues that may point to a renal diagnosis other than kidney disease due to diabetes. Such individuals should undergo an appropriate assessment for the cause of their disease. Table 2 also lists some conditions whose presence would prompt a referral to a renal specialist.

Although 24-hour collections are not needed for routine screening in diabetes, they can be useful when there is doubt about the accuracy of an eGFR, when screening for non-albumin urinary proteins (e.g. multiple myeloma) or when estimating daily sodium intake in an individual with refractory edema or hypertension. Individuals should be counseled to discard the first morning urine on the day of collection, and then collect all subsequent urine for a 24-hour period, including the first morning urine of the next day.

Screening for CKD

People with diabetes should undergo annual screening for the presence of diabetes-related kidney disease when they are clinically stable and not suspected to have non-diabetic kidney disease or an AKI. Screening should be delayed in the presence of conditions that can cause transient albuminuria or a transient fall in eGFR. Screening for CKD in people with diabetes should be performed with a random urine ACR and a serum creatinine that is then converted into an eGFR. This can be delayed five years from the onset of type 1 diabetes, but should begin immediately at the time of diagnosis of type 2 diabetes. An abnormal screening test should be confirmed by repeat testing of the eGFR in three months, and up to two more random urine ACRs ordered during that interval. If either the eGFR remains low or at least two of the three random urine ACRs are abnormal, then a diagnosis of CKD is confirmed. The exception to this approach is when the random urine ACR indicates albuminuria in the overt kidney disease range (≥20.0 mg/mmol/L), as this level of proteinuria rarely resolves spontaneously, and repeat testing is usually unnecessary.

Once a diagnosis of CKD has been made, a urine sample for dipstick and microscopy for casts or hematuria should be performed. In addition, serum electrolytes should be ordered along with any other testing that is indicated. In the absence of any significant abnormalities other than proteinuria or an isolated low eGFR, a presumptive diagnosis of kidney disease due to diabetes is made. The presence of clinical or laboratory abnormalities suggesting non-diabetic kidney disease indicates the need for appropriate work-up or referral (see Recommendation 9 for more details).

Prevention, Treatment and Follow Up

Glycemic control

Optimal glycemic control established as soon after diagnosis as possible will reduce the risk of development of diabetic kidney disease (44–48). The progression of renal damage in diabetes can be slowed through intensive glycemic control (44,49). The optimal target glycated hemoglobin (A1C) remains controversial. The major studies supporting renal protection achieved an A1C of about 7% in the intensively managed groups (Diabetes Control and Complications Trial [DCCT], Kumamoto, United Kingdom Prospective Diabetes Study [UKPDS], and Veterans Affairs Diabetes Trial [VADT]) (48,50–52). The Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation [ADVANCE] study demonstrated a reduction of progression of nephropathy with a target A1C <6.5% (53), as did the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial with a target A1C of <6.0% (54,55). However, none of these studies demonstrated a reduction in cardiovascular (CV) events or mortality with intensive glycemic control and, indeed, ACCORD was stopped early due to an increase in CV events in the intensive group. This indicates that the optimal A1C may differ for microvascular vs. CV events. Hypoglycemia is more common as progressively lower A1C levels are targeted (56), and people with CKD are at an increased risk of hypoglycemia (57,58). For most adults with diabetes, a target A1C of <7.0% is recommended for renal protection. For some people with early or no kidney disease and a low risk of hypoglycemia, a lower A1C can be considered for renal protection, with consideration of the risks vs. benefits (see Targets for Glycemic Control chapter, p. S42). It should be noted that these studies examined people with early renal disease and diabetes. Evidence supporting intensive glycemic control is lacking in people with advanced renal dysfunction. The A1C can be falsely low in people with advanced renal functional impairment, in particular those receiving intravenous iron or an erythropoiesis stimulating agent (59,60) (see Monitoring Glycemic Control chapter, p. S47).

Blood pressure control

Optimal BP control also appears to be important in the prevention and progression of CKD in diabetes, although the results have

been less consistent (47,51,61–63). The UKPDS study suggested that a target BP of <150/85 mmHg was associated with a reduction in microvascular events, including renal outcomes (51). The Systolic Hypertension in Europe (Syst-Eur) trial also found that a target systolic BP of <150 mmHg was associated with fewer people developing proteinuria among those with diabetes, and in the overall study group was associated with fewer people developing a creatinine >177 mmol/L (64). The Appropriate Blood Pressure Control in Diabetes (ABCD) normotensive study found that achieving a systolic BP of <130 mmHg was associated with fewer people developing microalbuminuria and, among those starting with microalbuminuria, a reduced risk of progressing to macroalbuminuria (65). The Lewis study in type 1 diabetes found that a target mean arterial pressure of 92 mmHg (125/75) was associated with a reduction in proteinuria (66). The ACCORD BP study also found less progression of proteinuria when targeting a systolic BP <120 mmHg (67). However, none of these studies demonstrated a meaningful impact on loss of renal function or ESRD and, indeed, ACCORD suggested that there were more acute kidney injury events in the intensive control group. We recommend that, for most people with diabetes, a target BP <130/80 mmHg is sufficient for renal protection (see Treatment of Hypertension chapter, p. S186).

Blockade of the renin angiotensin aldosterone system

Blockade of the renin angiotensin aldosterone system (RAAS) with either an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) can reduce the risk of developing CKD in diabetes independent of their effect on BP. This protective effect has been demonstrated in people with diabetes and hypertension (68,69), but not in normotensive people with diabetes (70–72). Additionally, progression of CKD in diabetes can be slowed through the use of an ACE inhibitor or ARB (72), independent of their effect on BP, and these two medication classes appear to be equally effective for cardiorenal protection (73,74). In type 1 diabetes, ACE inhibitors have been shown to decrease albuminuria and prevent worsening of nephropathy (75), and ARBs have been shown to reduce albuminuria (76). In type 2 diabetes, ACE inhibitors and ARBs have been shown to decrease albuminuria and prevent worsening of kidney disease, and ARBs have been shown to delay the time to dialysis in those with renal dysfunction at baseline (69,77–80). These renal-protective effects also appear to be present in proteinuric individuals with diabetes and normal or near-normal BP. ACE inhibitors have been shown to reduce progression of diabetic kidney disease in albuminuric normotensive individuals with both type 1 (81–84) and type 2 diabetes (85,86).

In CKD from causes other than diabetic kidney disease, ACE inhibition has been shown to reduce albuminuria, slow progression of renal disease, and delay the need for dialysis (87,88). The effectiveness of ACE inhibitors and ARB on loss of renal function appear to be similar in non-diabetic CKD (89,90).

A variety of strategies to more aggressively block the RAAS have been studied in kidney disease, including combining RAAS blockers or using very high doses of a single RAAS blocker. These strategies reduce albuminuria, but have not been proven to improve patient outcomes in diabetic nephropathy (91–96), and come at a risk of increased acute renal failure, typically when a patient develops intravascular volume contraction (97,98) and hyperkalemia. The lack of meaningful impact on loss of renal function through dual RAAS blockade was demonstrated in three randomized controlled trials, including the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) which examined a low renal risk population (97); and the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study (98) and Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study (99) which examined people with CKD in diabetes and high renal risk. As a result of these studies, combination of agents that block the RAAS (ACE inhibitor, ARB, direct renin inhibitor [DRI]) should not be used in the management of diabetes and CKD. The impact of adding a mineralocorticoid receptor antagonist to background standard of care including an ACE inhibitor or ARB is being evaluated in the Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD) (ClinicalTrials.gov Identifier NCT02540993) and Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD) (ClinicalTrials.gov Identifier NCT02545049) trials and with further evaluate the role of dual RAAS inhibition.

Other interventions

All people with CKD are at risk for CV events, and should be treated to reduce these risks (100–103) (see Cardiovascular Protection in People with Diabetes chapter, p. S162). The degree of risk of CV events or progression to ESRD increases as albuminuria levels rise, and as eGFR falls, with the combination of albuminuria and low eGFR predicting a very high level of risk (104,105).

Three recent CV trials of antihyperglycemic agents in participants with type 2 diabetes with high CV risk have shown renal benefits. The Empagliflozin Cardiovascular Outcome Event (EMPA-REG OUTCOME) Trial examined an SGLT2 inhibitor in people with CVD and generally well preserved eGFR (one-third had eGFR 30–60 mL/min/1.73 m^2, and one-third had albuminuria) and found a 39% reduction in worsening kidney disease (secondary endpoint: macroalbuminuria, doubling of creatinine, dialysis or renal death) and a slower rate of eGFR decline vs. placebo (106). The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program trial examined an SGLT2 inhibitor in high CV risk type 2 diabetes. The average eGFR was 76.5 mL/min/1.73 m^2 and the median ACR was 1.4 mg/mmol. Again, there was a 40% reduction in worsening kidney disease (secondary endpoint: 40% reduction in GFR, renal replacement therapy or renal death) (107). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial examined a GLP-1 receptor agonist in people with CV disease, CKD or CV risk factors (one-quarter had eGFR 30 to 60 mL/min/1.73 m^2) and showed a 22% reduction in worsening kidney disease (in particular, reducing the new onset of persistent macroalbuminuria) vs. placebo, but this result was explained by reduction in the new onset of persistent macroalbuminuria rather than effect on doubling of the serum creatinine level, ESRD incidence, or death due to renal disease (108,109). In contrast to the GLP-1 receptor agonist trial in which hard renal outcomes were not improved, results from the two independent SGLT2 inhibitor trials showed significant hard renal outcome benefit. Of note, the presence of CKD (stage 3 or lower) should not preclude the use of either of these beneficial therapies, although the glucose-lowering efficacy of SGLT2 inhibitors is attenuated (as the A1C reduction is proportional to the level of GFR).

Treating Kidney Disease Safely

The "sick-day" medication list

Several classes of medications used commonly in people with diabetes can reduce kidney function during periods of intercurrent illness, and should be discontinued when a person is unwell, in particular, when they develop significant intravascular volume contraction due to reduced oral intake or excessive losses due to vomiting or diarrhea. Diuretics can exacerbate intravascular volume contraction during periods of intercurrent illness. Blockers of the

RAAS interfere with the kidney's response to intravascular volume contraction, namely the ability of angiotensin II to contract the efferent arteriole to support glomerular filtration during these periods. Non-steroidal anti-inflammatories (NSAIDs) cause constriction of the afferent arterioles, which can further reduce blood flow into the glomerulus, especially in people who are volume contracted. For these reasons, all of these drugs can reduce kidney function during times of intercurrent illness. Consideration should be given to providing people with a "sick-day" medication list, instructing the patient to hold these medications if they feel that they are becoming dehydrated for any reason. A number of additional medications need to be dose-adjusted in people with renal dysfunction, and their usage and dosage should be re-evaluated during periods where kidney function changes (see Appendix 8. Sick-Day Medication List).

The safe use of RAAS blockers [ACEIs, ARBs, Aldosterone Antagonists (AAs) and Direct Renin Inhibitors (DRIs)]

Drugs that block the RAAS reduce intraglomerular pressure which, in turn, leads to a rise in serum creatinine of up to 30% which then stabilizes (110). Although these drugs can be used safely in people with ischemic nephropathy, these people may have an even larger rise in serum creatinine when these drugs are used (111–113). In the case of severe renal artery stenosis that is bilateral (or unilateral in a person with a single functioning kidney), RAAS blockade can precipitate renal failure. In addition, RAAS blockade can lead to hyperkalemia. People with diabetes and CKD are at a particularly high risk for this complication (114,115). This risk is highest with aldosterone antagonists (AAs), and the use of AAs without careful monitoring of potassium has been associated with an increase in hospitalization and death associated with hyperkalemia (116).

For these reasons, the serum creatinine and potassium should be checked between one and two weeks after initiation or titration of a RAAS blocker (113). In people where a significant change in creatinine (decrease in eGFR >30%) or potassium are seen, further testing should be performed to ensure that these tests have stabilized. Mild to moderate hyperkalemia can be managed through dietary counseling. Diuretics, in particular furosemide, can increase urinary potassium excretion. Sodium bicarbonate (500 to 1,300 mg orally twice a day) can also increase urinary potassium excretion, especially amongst individuals with a metabolic acidosis as demonstrated by a low serum bicarbonate level. If hyperkalemia is severe, RAAS blockade would need to be held or discontinued (117) and advice should be sought from a renal specialist.

As the use during pregnancy of RAAS blockers has been associated with congenital malformations (118), women with diabetes of childbearing age should avoid pregnancy if drugs from these classes are required. If a woman with diabetes receiving such medications wishes to become pregnant, then these medications should be discontinued prior to conception (see Diabetes and Pregnancy chapter, p. S255).

Antihyperglycemic Medication Selection and Dosing in CKD

Many antihyperglycemic medications need to have their dose adjusted in the presence of low renal function, and some are contraindicated in people with significant disease. See Figure 1 in Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88 and Appendix 7. Therapeutic Considerations for Renal Impairment.

Referral to a Specialized Renal Clinic

Most people with CKD and diabetes will not require referral to a specialist in renal disease and can be managed in primary care. However, specialist care may be necessary when renal dysfunction is severe, when there are difficulties implementing renal-protective strategies or when there are problems managing the sequelae of renal disease (119) (see Recommendation 8 for more details).

RECOMMENDATIONS

1. To prevent the onset and delay the progression of CKD, people with diabetes should be treated to achieve optimal control of BG [Grade A, Level 1A (45,46) (see Recommendations 2 and 3, Targets for Glycemic Control chapter, p. S42) and BP [Grade A, Level 1A (61,65,96)].

2. In adults with diabetes, screening for CKD should be conducted using a random urine ACR and a serum creatinine converted into an eGFR [Grade D, Consensus]. Screening should commence at diagnosis of diabetes in individuals with type 2 diabetes and 5 years after diagnosis in adults with type 1 diabetes and repeated yearly thereafter [Grade D, Consensus].

3. A diagnosis of CKD should be made in people with an eGFR <60 mL/min/1.73 m^2 and/or random urine ACR ≥2.0 mg/mmol on at least 2 of 3 samples over a 3-month period [Grade D, Consensus].

4. All people with diabetes and CKD should receive a comprehensive, multifaceted approach to reduce CV risk [Grade A, Level 1A (101,103)] (see Cardiovascular Protection in People with Diabetes chapter, p. S162).

5. Adults with diabetes and CKD with either hypertension or albuminuria should receive an ACE inhibitor or an ARB to delay progression of CKD [Grade A, Level 1A for ACE inhibitor use in type 1 and type 2 diabetes, and for ARB use in type 2 diabetes (69,75,77–81,84–86); Grade D, Consensus for ARB use in type 1 diabetes].

6. People with diabetes on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked at baseline and within 1 to 2 weeks of initiation or titration of therapy and during times of acute illness [Grade D, Consensus].

7. Adults with diabetes and CKD should be given a "sick-day" medication list that outlines which medications should be held during times of acute illness (see Appendix 8. Sick-Day Medication List) [Grade D, Consensus].

8. Combinations of ACE inhibitor, ARB or DRI should not be used in the management of diabetes and CKD [Grade A, Level 1 (95,98)].

9. People with diabetes should be referred to a specialist with expertise in CKD in the following situations [Grade D, Consensus for each of the following]:
   a. Chronic, progressive loss of kidney function
   b. Urine ACR persistently >60 mg/mmol
   c. eGFR <30 mL/min
   d. Unable to remain on renal-protective therapies due to adverse effects, such as hyperkalemia or a >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB
   e. Unable to achieve target BP.

10. In adults with type 2 diabetes with clinical CVD in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m^2, an SGLT2 inhibitor with proven renal benefit may be considered to reduce the risk of progression of nephropathy [Grade B, Level 2 (106) for empagliflozin; Grade C, Level 3 (107) for canagliflozin].

Abbreviations:
A1C, glycated hemoglobin; *ACE*, angiotensin converting enzyme; *AA;* aldosterone antagonists; *ARB*, angiotensinogen *receptor blocker; ACR*, albumin creatinine ratio; *BP*, blood pressure; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DRI;* direct renin inhibitor; *eGFR*, estimated glomerular filtration rate; *ESRD*, end stage renal disease; *GFR;* glomerular filtration rate; *NSAIDs; n*on-steroidal anti-inflammatories; *RAAS;* renin angiotensin aldosterone system.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Monitoring Glycemic Control, p. S47

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Treatment of Hypertension, p. S186
Diabetes and Pregnancy, p. S255

Relevant Appendices

Appendix 7. Therapeutic Considerations for Renal Impairment
Appendix 8. Sick-Day Medication List

Related Websites

Alberta Chronic Kidney Disease (CKD) Clinical Pathway (available at http://www.renalnetwork.on.ca/hcpinfo/guidelines_and_resources/kidneywisetoolkit/)
Ontario Renal Network: KidneyWise Clinical Toolkit (available at http://www.renalnetwork.on.ca/hcpinfo/guidelines_and_resources/kidneywisetoolkit/)

Author Disclosures

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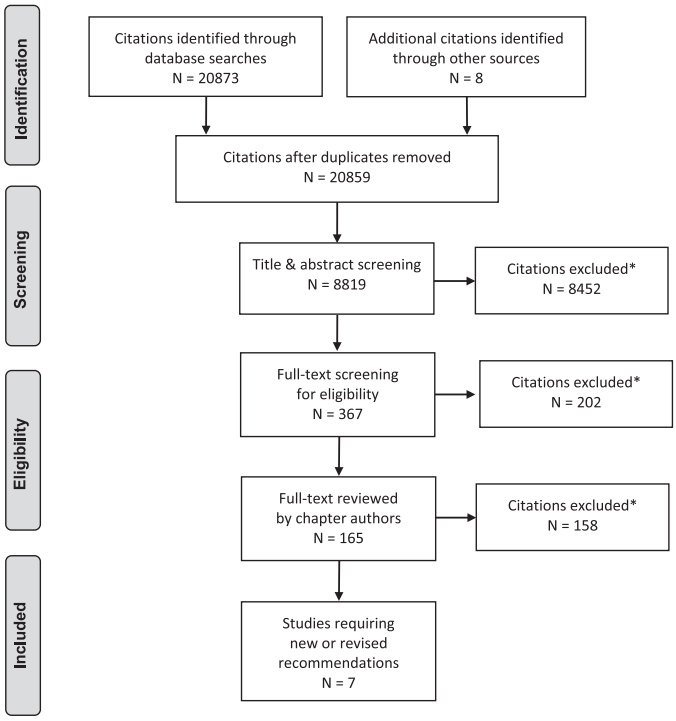
Literature Review Flow Diagram for Chapter 29: Chronic Kidney Disease in Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design

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2018 Clinical Practice Guidelines

Retinopathy

Diabetes Canada Clinical Practice Guidelines Expert Committee

Filiberto Altomare MD, FRCSC, Amin Kherani MD, FRCSC, Julie Lovshin MD, FRCPC

KEY MESSAGES

- Regular screening is important for early detection of treatable diabetic retinopathy. Screening intervals for diabetic retinopathy vary according to the individual's age and type of diabetes.
- Optimal glycemic control reduces the onset and progression of sight-threatening diabetic retinopathy.
- Local intraocular pharmacological therapies have the potential to improve vision and reduce the level of retinopathy.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Diabetic retinopathy involves changes to retinal blood vessels that can cause them to bleed or leak fluid, distorting vision.
- With good glycemic control, regular eye exams and early treatment, the risk of vision loss is reduced.
- Diabetic retinopathy often goes unnoticed until vision loss occurs; therefore, people with diabetes should get a comprehensive dilated eye exam regularly. Discuss the recommended frequency with your diabetes healthcare team and experienced vision care professionals (optometrists or ophthalmologists).
- Diabetic retinopathy can be treated with several therapies used alone or in combination.

Introduction

Diabetic retinopathy is the most common cause of incident blindness (legal) in people of working age (1). The Eye Diseases Prevalence Research Group determined the crude prevalence rate of retinopathy in the adult population with diabetes of the United States to be 40.3%; sight-threatening retinopathy occurred at a rate of 8.2% (1). Previous data showed the prevalence rate of proliferative retinopathy to be 23% in people with type 1 diabetes, 14% in people with type 2 diabetes on insulin therapy and 3% in people receiving noninsulin antihyperglycemic therapies (2). Macular edema occurs in 11%, 15% and 4% of these groups, respectively (3). Higher prevalence rates have been noted in Indigenous populations in Canada (4,5).

Visual loss is associated with significant morbidity, including increased falls, hip fracture and a 4-fold increase in mortality (6). Among individuals with type 1 diabetes, limb amputation and visual loss due to diabetic retinopathy are independent predictors of early death (7).

Definition and Pathogenesis

Diabetic retinopathy is clinically defined, diagnosed and treated based on the extent of retinal vascular disease detected by ophthalmoscopy. Three distinct forms of diabetic retinopathy are described: 1) macular edema, which includes diffuse or focal vascular leakage at the macula; 2) progressive accumulation of microvascular change that includes microaneurysms, intraretinal hemorrhage, vascular tortuosity and vascular malformation (together known as nonproliferative diabetic retinopathy) that ultimately leads to abnormal vessel growth on the optic disc or retina (proliferative diabetic retinopathy); and 3) retinal capillary nonperfusion, a form of vascular closure detected on retinal angiography, which is recognized as a potential complication associated with diabetes that can cause blindness and currently has no treatment (albeit ameliorated by ranibizumab therapy) (8).

Screening

Sight-threatening diabetic retinopathy includes severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy or foveal threatening diabetic macular edema (DME) evaluated either clinically and/or by optical coherence tomography (OCT) modalities. Clinically significant diabetic macular edema (CSME) is a strictly defined term determined by subjective biomicroscopy assessment of retinal thickening of the area and distance from the foveal centre (the centre of the macula responsible for high-acuity vision), with or without hard exudates (9). Use of OCT technology more accurately measures and quantifies retinal thickening threatening the foveal centre; this imaging modality has encouraged the terminology "centre-involving" DME to guide therapeutic decisions.

Since therapies are available for sight-threatening diabetic retinopathy, which reduce the risk of blindness, ophthalmic screening strategies are necessary to identify treatable disease (9–13). Screening can be performed with dilated ophthalmoscopy, fundus imaging (photography—preferably standard 7 field or wide field imaging +/- macular OCT) combined with telehealth systems by qualified vision care professionals (ideally optometrists or ophthalmologists). With improved multimodal treatment options, including intraocular injectable pharmaceuticals, laser modalities

Conflict of interest statements can be found on page S214.

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Table 1
Screening for retinopathy

When to initiate screening
• Type 1 diabetes: 5 years after diagnosis in all individuals ≥15 years
• Type 2 diabetes: children, adolescents and adults at diagnosis
Screening methods
• 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard)
• Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil
• Digital fundus photography
If retinopathy is present
• Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)
• Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy
• Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
• Screen for other diabetes complications
If retinopathy is not present
• Type 1 diabetes: rescreen annually
• Type 2 diabetes: rescreen every 1 to 2 years
• Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
• Screen for other diabetes complications

BP, blood pressure.
* See Targets for Glycemic Control chapter, p. S42; Hypertension chapter, p. S186; Dyslipidemia chapter, p. S178

and microsurgical advances, appropriate screening, careful retinopathy grading and timely referral for management cannot be overemphasized to prevent treatable vision loss.

Screening recommendations take into account the differences in incidence and prevalence of retinopathy observed in type 1 and type 2 diabetes, and in children and adults (Table 1) (14–19).

Diabetic retinopathy rarely develops in children with type 1 diabetes <10 years of age regardless of the duration of diabetes (18). Among people <15 years of age, irrespective of age of onset of diabetes, the prevalence of mild nonproliferative retinopathy was 2%, and none had sight-threatening diabetic retinopathy (10,18). However, the prevalence rate increases sharply after 5 years' duration of diabetes in postpubertal individuals with type 1 diabetes (18). In the Wisconsin Epidemiology Study of Diabetic Retinopathy 4-year incidence study, no person <17 years of age developed proliferative retinopathy or macular edema (16,20,21). Screening frequency for retinopathy has been extensively evaluated through post-hoc statistical modelling of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC), and results suggest that frequency can be individualized based on retinopathy stage and current A1C level. However, modification of current recommendations for annual screening will require confirmation in an independent study and demonstration that these findings can be translated into practice safely and effectively. Controversy, therefore, exists on whether the ideal approach to screening is a population-wide screening program with regular intervals or the development of personalized protocols.

In people with type 2 diabetes, retinopathy may be present in 21% to 39% soon after clinical diagnosis, but is sight-threatening in only about 3% (3,17,19,22). In the United Kingdom Prospective Diabetes Study (UKPDS), few participants without retinopathy at diagnosis of diabetes had disease progression to the point of requiring retinal photocoagulation (laser treatment) in the following 3 to 6 years (23). More recently, progression rates of diabetic retinopathy were prospectively evaluated (14,15,24). The Liverpool Diabetic Eye Study reported the 1-year cumulative incidence of sight-threatening diabetic retinopathy in individuals with type 1 or type 2 diabetes who, at baseline, had no diabetic retinopathy, had background retinopathy or had mild preproliferative retinopathy. In people with type 1 diabetes, the incidence in these groups was 0.3%, 3.6% and 13.5%, respectively (14) and, in type 2 diabetes individuals, it was 0.3%, 5.0% and 15.0%, respectively (15). Although the incidence of sight-threatening diabetic retinopathy in the group without baseline diabetic retinopathy is low (14,15,23,24), there have been no studies comparing various screening intervals in their effectiveness to reduce the risk of vision loss (25).

Telemedicine programs relying on fundus photography are widely used in Canada and internationally for the identification and triage of people with diabetic retinopathy (26). This has been greatly facilitated by the advent of high-resolution ultra-wide field imaging (UWFI). The Joslin Vision Network, an ocular telehealth program at the Joslin Diabetes Center, demonstrated that UWFI employed by trained certified imagers adhering to defined imaging and grading protocols, accurately evaluated images for the presence of diabetic retinopathy or diabetic retinopathy that required referral for prompt ophthalmic care, with a sensitivity and negative predictive value approaching 1.0 (27). Furthermore, UWFI technology has permitted the identification of peripheral diabetic retinal lesions, missed by standard 7-field fundus photography, that more accurately identifies the severity level of diabetic retinopathy and the risk of retinopathy progression over 4 years (28).

Delay of Onset and Progression

Risk factors for the development or progression of diabetic retinopathy are longer duration of diabetes, elevated A1C, increased blood pressure (BP), dyslipidemia, anemia, pregnancy (with type 1 diabetes), proteinuria and severe retinopathy itself (1,16–19,21,29–34) (see Diabetes and Pregnancy chapter, p. S255).

Glycemic control

Optimizing glycemic control, targeting an A1C ≤7%, is recommended to slow the development and progression of diabetic retinopathy (see Targets for Glycemic Control chapter, p. S42). The DCCT and the UKPDS demonstrated that intensive glycemic control (A1C <7%) reduced both the development and progression of retinopathy (35–37), with the beneficial effects of intensive glycemic control persisting for up to 10 years after completion of the initial trials (38,39). Two studies examined the effect of more aggressive BG (blood glucose) lowering (A1C <6.5%) in people with established type 2 diabetes (duration 6 to 10 years). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study, intensive glycemic control was associated with a lower rate of retinopathy progression than standard therapy (40,41), while in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Retinal Measurements study (AdRem), intensive glycemic control did not significantly reduce development or progression of retinopathy (42). In type 1 diabetes, rapid improvement of glycemia may be associated with transient early worsening of retinopathy, but this effect is offset by long-term benefits (43).

BP control

BP control is an important component of risk factor modification in diabetes and reduces the risk of retinopathy progression (see Treatment of Hypertension chapter, p. S186). The UKPDS showed that, among people with newly diagnosed type 2 diabetes, BP control (target BP <150/85 mmHg, actual BP 144/82 mmHg) resulted in a significant reduction in retinopathy progression, as well as a decrease in significant visual loss and requirement for laser therapy compared to less control (target BP <180/105 mmHg, actual mean BP 154/87 mmHg) (44). The ACCORD and ADVANCE studies examined

more aggressive BP lowering in people with established type 2 diabetes. In both these studies, where mean BP was <140/80 mmHg in both the active intervention and control groups, active treatment did not show additional benefit vs. standard therapy. However, in the ADVANCE study data set, analysis of visit-to-visit variability of systolic BP and maximum systolic BP were predictive of diabetic retinopathy complications independent of mean BP (45). In contrast, in type 1 diabetes, the DCCT trial did not show variability of BP as a risk factor for diabetic retinopathy (46).

Although a number of clinical trials have examined the effect(s) of renin angiotensin aldosterone system (RAAS) blockade on retinopathy progression or development among normotensive people with diabetes, the results have generally been conflicting or inconclusive. In the Renin-Angiotensin System Study (RASS), involving 223 normotensive, normoalbuminuric participants with type 1 diabetes, neither the angiotensin-converting enzyme (ACE) inhibitor, enalapril, or the angiotensin receptor blocker (ARB), losartan, reduced retinopathy progression independent of BP change (47). The Diabetic Retinopathy Candesartan Trials (DIRECT) program, involving 5,231 participants, evaluated the effect of the angiotension II type 1 ARB candesartan 32 mg daily on the incidence of retinopathy in participants with type 1 diabetes (DIRECT-Prevent 1) (48) and on the progression of retinopathy in participants with either type 1 diabetes (DIRECT-Protect 1) (48) or type 2 diabetes (DIRECT-Protect 2) (49). The DIRECT studies did not meet their primary endpoints, although there was an overall change toward less severe retinopathy with candesartan (48,49).

In view of the conflicting data, a systematic review and meta-analysis was carried out to evaluate the effect(s) of RAAS inhibition on diabetic retinopathy, and to compare between ACE inhibitors and ARBs (50). The study included 21 randomized controlled clinical trials and 13,823 participants. Results of these analyses suggest that RAAS inhibition was associated with reduced risk of incidence and progression of diabetic retinopathy, and that ACE inhibitors were better than ARBs at reducing these risks. However, the study did not evaluate the effect(s) of RAAS inhibition in participants with multiple medical comorbidities (the subgroup of participants that are more likely to benefit from RAAS blockade), or the optimal dosage and duration of specific RAAS inhibitors. Thus, while BP lowering (including use of RAAS blockers) reduces retinopathy rates and is an important component of cardiovascular (CV) protection (see Cardiovascular Protection in People with Diabetes chapter, p. S162), there is insufficient evidence to recommend specific routes of RAAS blockade as primary prevention for retinopathy for all normotensive people with diabetes.

Lipid-lowering therapy

Dyslipidemia is an independent risk factor for retinal hard exudates and CSME in type 1 diabetes (24,51). While statin-based lipid-lowering therapies are an integral part of CV protection in diabetes, the role of these agents in preventing the development or progression of retinopathy has not been established (37,52). The role of the peroxisome proliferator-activated receptor-alpha agonist fenofibrate has been assessed in 2 large-scale randomized controlled trials. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate 200 mg daily reduced both the requirement for laser therapy (a pre-specified tertiary endpoint) and retinopathy progression among people with pre-existing retinopathy (53). In the ACCORD Eye study, the addition of fenofibrate 160 mg daily to simvastatin was associated with a 40% reduction in the primary outcome of retinopathy progression over 4 years (40,41). From the study's control and event rates, the number of people needed to treat with combination statin and fenofibrate therapy to prevent 1 retinopathy progression event is estimated at 27 over the 4-year period. The mechanism for any beneficial effect of fenofibrate in diabetic retinopathy has not been established. Active treatment with fenofibrate was associated with an increase in high-density lipoprotein cholesterol (HDL-C) and decrease in serum triglycerides in ACCORD Eye (40,41); however, in the FIELD study, any beneficial effect of fenofibrate was independent of plasma lipid concentrations (53). Thus, the addition of fenofibrate to statin therapy could be considered in people with type 2 diabetes to slow the progression of established retinopathy.

Antiplatelet therapy

Systematic review suggests that acetylsalicylic acid (ASA) therapy neither decreases or increases the incidence or progression of diabetic retinopathy (54). Correspondingly, ASA use does not appear to be associated with an increase in risk of vitreous hemorrhage or DME (55,56).

Treatment

Treatment modalities for diabetic retinopathy include retinal photocoagulation, intraocular injection of pharmacological agents and vitreoretinal surgery.

Laser therapy

As determined in the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS), panretinal laser photocoagulation to the retinal periphery reduces severe visual loss and reduces legal blindness by 90% in people with severe nonproliferative or proliferative retinopathy (10–12). As determined by the ETDRS, focal laser treatment to the macula for CSME reduces the incidence of moderate visual loss by 50% (9). Long-term follow-up studies to the original laser photocoagulation trials confirm its benefit over several decades (57).

Local (intraocular) pharmacological intervention

The cytokine, vascular endothelial growth factor (VEGF), is a potent vascular permeability and angiogenic factor. Increased VEGF expression has been demonstrated to play a pivotal role in the development of diabetic retinopathy and, in particular, DME. Treatment of centre-involving DME with intravitreal anti-VEGF agents has been associated with improved vision and reduction of macular edema (thickening), unlike focal macular laser where the effect is to reduce the probability of further vision loss. Thus, anti-VEGF drugs have become first-line therapy in the management of centre-involving DME, and focal macular laser continues to be used when central vision is not involved. Three anti-VEGF agents are available, namely, ranibizumab, aflibercept and off-label use of bevacizumab.

Two masked, phase III, randomized clinical trials, A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RISE) and A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema (ME) With Center Involvement Secondary to Diabetes Mellitus (RIDE), using monthly ranibizumab, a humanized recombinant anti-VEGF antibody fragment, with or without prompt laser, improved visual acuity compared against sham over the 2 years of study (58). In the RISE trial, 44% and 39% of participants receiving 0.3 or 0.5 mg ranibizumab, respectively, gained 15 letters or more (3 lines) of acuity vs. 18% of those in the control arm. In the RIDE study, 33% or 45% of participants gained 15 letters or more at doses of 0.3 or 0.5 mg, respectively. RISE and RIDE open-label extension trials showed visual acuity

gains and safety profiles were maintained with a marked reduction in subsequent treatment frequency (59).

Furthermore, 1-year results of a phase III clinical trial, Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema (RESTORE), using an initial loading dose of 3 monthly injections of 0.5 mg ranibizumab, and as-needed treatment thereafter, likewise demonstrated improvement in the primary and secondary outcome measures of best corrected visual acuity and reduction in central macular thickness. In all studies, the effect(s) of ranibizumab were consistent when used as monotherapy or in conjunction with macular photocoagulation. In the RESTORE study, 37% to 43% of ranibizumab-treated participants improved vision by 10 letters or more compared to 16% with focal macular laser (60). Three-year extension results maintained similar outcomes (61).

Similar positive results were obtained by the Diabetic Retinopathy Clinical Research Network (DRCR.net) (Protocol I - 5-year results) using flexible ranibizumab plus prompt or deferred laser treatment algorithms (62,63).

Aflibercept is a recombinant fusion protein comprised of the highest-affinity binding site from VEGF receptor 1 and 2, fused to the constant region (Fc) of immunoglobulin G1, and binds or traps VEGF and PlGF (Placental Growth Factor). Two masked phase III randomized clinical trials, Study of Intravitreal Aflibercept Injection in Patients With Diabetic Macular Edema (VISTA DME) and Intravitreal Aflibercept Injection in Vision Impairment Due to DME (VIVID-DME), evaluated aflibercept at 2 different dosing intervals (2q4 and 2q8) vs. macular laser photocoagulation. The 52-week visual and anatomic superiority of aflibercept over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups. Mean BCVA gain from baseline to week 100 with aflibercept 2q4, 2q8 and laser control was 11.5, 11.1 and 0.9 letters ($p<0.0001$) in VISTA and 11.4, 9.4 and 0.7 letters ($p<0.0001$) in VIVID, respectively (64).

A similar outcome was noted when comparing intraocular injection of bevacizumab (a full-length antibody against VEGF) to macular laser. Two-year results of A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT), a phase 3 clinical trial, demonstrated a gain of at least 15 letters or more in 32% of participants receiving 1.25 mg bevacizumab compared to 4% in the control arm (65). However, unlike ranibizumab and aflibercept, intraocular injection of bevacizumab in diabetic retinopathy constitutes off-label use of the drug in Canada.

A head-to-head randomized clinical trial, Diabetic Retinopathy Clinical Research Network Protocol T study, was carried out comparing the 3 anti-VEGF agents—aflibercept, bevacizumab and ranibizumab—in the treatment of centre-involving DME. All 3 agents demonstrated improvement of visual acuity and reduction in central macular thickness both at year 1 (66) and year 2. Superiority of aflibercept was noted in the group of participants with worse baseline visual acuity. This superiority of aflibercept at year 2 with gains of 18.1 letters in aflibercept, 13.3 letters in bevacizumab and 16.1 letters in ranibizumab groups at 2 years (aflibercept vs. bevacizumab, $p=0.02$, aflibercept vs. ranibizumab, $p=0.18$, and ranibizumab vs. bevacizumab, $p=0.18$).

Steroids are an alternate class of drug utilized in the management of DME. Injectable agents include triamcinolone, dexamethasone and fluocinolone.

Intravitreal injection of triamcinolone combined with prompt macular laser was as effective as ranibizumab in a single subgroup of people characterized by previous cataract surgery (62).

The Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study group showed positive visual results with the dexamethasone (DEX) implant over a 3-year follow-up period. The percentage of participants with ≥15-letter improvement in BCVA from baseline at study end was greater with DEX implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12.0%, $p\leq0.018$) (67).

The fluocinolone implant for DME has been studied (68,69) and more recently was studied vs. sham in the Fluocinolone Acetonide for Macular Edema (FAME) study, a phase III clinical trial consisting of 2 3-year pivotal trials. The percentage of participants with improvement from baseline letter score of 15 or more at month 24 was 28.7% and 28.6% in the low- and high-dose insert groups, respectively, compared with 16.2% in the sham group ($p=0.002$ for each) (70).

However, treatments with intraocular steroids are associated with increased rates of glaucoma and cataract formation.

Randomized-controlled trials evaluating anti-VEGF therapy for the treatment of centre-involving DME have noted improved diabetic retinopathy severity scale (DRSS). Progression of DRSS severity has been associated with an increased risk of development of proliferative diabetic retinopathy and DME (71). In nonproliferative diabetic retinopathy, ranibizumab (RISE/RIDE phase IV trial) demonstrated ≥2 step improvement in DRSS at year 3 ($p=0.0003$). Similarly, with aflibercept, a significant proportion of eyes demonstrated ≥2 step improvement in DRSS in the VISTA trial ($p=0.0001$) and VIVID trial ($p=0.0004$) (64). In proliferative diabetic retinopathy, ranibizumab demonstrated to be not inferior to PRP (panretinal photocoagulation) with 47% of eyes demonstrating ≥2 step improvement in DRSS (72). Thus, future randomized controlled trials may further evaluate DRSS as a primary endpoint in the prevention or regression of diabetic retinopathy.

Surgical intervention

Vitreoretinal surgery in diabetes is necessary for retinopathy complicated with non-clearing vitreous bleeding, persistent neovascularization (especially post PRP laser +/- VEGF injectables) and vitreoretinal traction, especially with retinal detachment threatening the macula. The Diabetic Retinopathy Vitrectomy Study (DRVS) Group evaluated the benefit of early vitrectomy (<6 months) in the treatment of severe vitreous hemorrhage (73) and very severe proliferative diabetic retinopathy (74). People with type 1 diabetes of <20 years' duration and severe vitreous hemorrhage were more likely to achieve good vision with early vitrectomy compared to conventional management (73). Similarly, early vitrectomy was associated with higher chance of visual recovery in people with either type 1 or 2 diabetes with very severe proliferative diabetic retinopathy (74). More recent surgical advances and instrumentation in vitrectomy since the DRVS trials have demonstrated reduced side effects with more consistent favourable visual outcomes, thus supporting vitrectomy in advanced proliferative diabetic retinopathy (75). Furthermore, these advances have expanded surgical indications to include earlier vitrectomy for diffuse macular edema, particularly with vitreomacular traction (76). It is worth noting that the use of perioperative ASA (77–79) and warfarin therapy (80) for persons undergoing ophthalmic surgery does not appear to raise the risk of hemorrhagic complications.

Overall, the last few years have seen significant advances in systemic, local and surgical treatments of diabetic eye disease, with significantly improved visual outcome. Most notably, long-term follow up to early laser studies confirm their sustained efficacy in preserving vision (57). Pharmacologic therapies, especially VEGF and steroid agents, demonstrate both preservation and recovery of vision in persons with DME. Despite these successes, it is important to encourage people with even moderate visual loss to seek assistance from community services that provide spectacle correction, enhanced magnification, vision aids and measures to encourage independence and ongoing quality of life (81,82).

RECOMMENDATIONS

1. In individuals ≥15 years of age with type 1 diabetes, screening and evaluation for retinopathy should be performed annually by an experienced vision care professional (optometrist or ophthalmologist) starting 5 years after the onset of diabetes [Grade A, Level 1 (16,18)] (for screening recommendation for children and adolescents <15 years with type 1 diabetes, see Type 1 Diabetes in Children and Adolescents chapter, p. S234; for screening recommendations for pregnant women, see Diabetes and Pregnancy chapter, p. S255).

2. In individuals with type 2 diabetes, screening and evaluation for diabetic retinopathy should be performed by an experienced vision care professional (optometrist or ophthalmologist) at the time of diagnosis of diabetes [Grade A, Level 1 (17,20)]. The interval for follow-up assessments should be tailored to the severity of the retinopathy [Grade D, Consensus]. In those with no or minimal retinopathy, the recommended interval is 1–2 years [Grade A, Level 1 (17,20)] (for screening recommendations for children and adolescents with type 2 diabetes, see Type 2 Diabetes in Children and Adolescents chapter, p. S247).

3. Screening for diabetic retinopathy should be performed by an experienced vision care professional (optometrist or ophthalmologist), either in person or through interpretation of retinal photographs taken through dilated pupils [Grade A, Level 1 (13)] or undilated pupils with high-resolution ultra-wide field imaging [Grade D, Consensus].

4. Results of eye examinations and the follow-up interval and plan should be clearly communicated to all members of the diabetes health-care team to promote optimal care [Grade D, Consensus].

5. To prevent the onset and delay the progression of diabetic retinopathy, people with diabetes should be treated to achieve optimal control of BG [Grade A, Level 1A (35,38) for type 1 diabetes; Grade A, Level 1A (36,40,41) for type 2 diabetes] and BP [Grade A, Level 1A (36,44) for type 2 diabetes; Grade D, Consensus for type 1 diabetes].

6. Although not recommended for CVD prevention or treatment, fenofibrate, in addition to statin therapy, may be used in people with type 2 diabetes to slow the progression of established retinopathy [Grade A, Level 1A (40,41,53)].

7. Individuals with sight-threatening diabetic retinopathy should be assessed by a qualified ophthalmologist and/or retina specialist [Grade D, Consensus]. Pharmacological intervention [Grade A, Level 1A (9,11,73,74)], laser therapy and/or vitrectomy [Grade A, Level 1A (58,60,68,69)] may be used to manage the diabetic retinopathy.

8. Visually disabled people should be referred for low-vision evaluation and rehabilitation [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *ACE;* angiotensin-converting enzyme; *ARB;* angiotensin receptor blocker; *BP*, blood pressure; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CSME*; clinically significant macular edema; *DHC*, diabetes health-care; *DME*, diabetic macular edema; *DRSS*, diabetic retinopathy severity scale; *HDL-C*; high-density lipoprotein cholesterol; *OCT*; optical coherence tomography; *PlGF*; placental growth factor; *PRP*, panretinal photocoagulation; *RAAS*; renin angiotensin aldosterone system; *VEGF*; vascular endothelial growth factor.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Dyslipidemia, p. S178
Treatment of Hypertension, p. S186
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255

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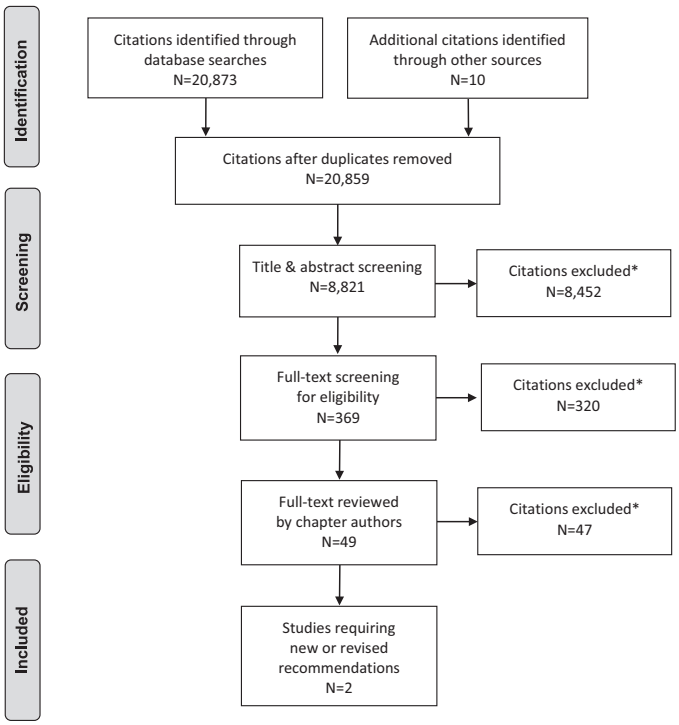
Literature Review Flow Diagram for Chapter 30: Retinopathy



*Excluded based on: population, intervention/exposure, comparator/control or study design

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (83).

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2018 Clinical Practice Guidelines

Neuropathy

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Elevated blood glucose levels, elevated triglycerides, high body mass index, smoking and hypertension are risk factors for neuropathy.
- Intensive glycemic control is effective for the primary prevention or secondary intervention of neuropathy in people with type 1 diabetes.
- In people with type 2 diabetes, lower blood glucose levels are associated with a reduced frequency of neuropathy.
- Simple physical examination screening tests, such as the 10 g monofilament (on the dorsal aspect of the great toe bilaterally) and vibration perception (with 128 Hz tuning fork), perform reasonably well for the identification of neuropathy and prediction of its future onset.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Exposure to high blood glucose levels over an extended period of time can cause diabetic peripheral neuropathy or damage to the nerves that go to the feet, legs and, when markedly advanced, to the hands and arms.
- The most common symptoms of diabetic peripheral neuropathy are loss of sensations in the toes and feet, and presence of symptoms, such as sharp shooting pains, burning, tingling, a feeling of being pricked with pins, throbbing and numbness.
- Diabetic peripheral neuropathy increases the risk for foot ulcers and amputation.
- Your health-care provider or foot care specialist can test for diabetic peripheral neuropathy by lightly pressing a thin nylon rod (10 g monofilament) and by using the 128 Hz tuning fork on the top surface of your big toe.
- Although there is no cure, there are many ways you can effectively manage diabetic peripheral neuropathy, including:
  - Proper foot care, including daily foot inspection
  - Effective blood glucose control
  - Medications that may help with nerve pain
- Diabetic autonomic neuropathies affect the part of the nervous system responsible for control of internal body functions and may target the heart (cardiac autonomic neuropathy), gastrointestinal tract, and genitourinary system, and can cause sexual dysfunction.

Introduction

Diabetes is the leading cause of neuropathy in North America (1). Estimates of the prevalence vary depending on the diagnostic criteria and population studied. A reasonable figure based on several large studies is that detectable sensorimotor polyneuropathy (diffuse and symmetric neuropathy) will develop within 10 years of the onset of diabetes in 40% to 50% of people with type 1 (1–3) and type 2 diabetes (4–6). While clinical neuropathy is uncommon in people with type 1 diabetes within the first 5 years after the onset of diabetes, people with type 2 diabetes may have neuropathy at the time of diagnosis or even in the prediabetes stage (4–7). Risk factors for neuropathy include elevated blood glucose (BG) levels, elevated triglycerides (TG), high body mass index (BMI), smoking and hypertension (8). There appear to be multifactorial mechanisms behind the pathogenesis of diabetic neuropathy (9) and it may represent a unique form of neurodegeneration (9,10).

The most common form of diabetic neuropathy is distal symmetric polyneuropathy (DSPN). Symptoms vary according to the class of sensory fibres involved. The most common early symptoms are from small fibre involvement and include pain (e.g. sharp, shooting) and dysesthesias (e.g. burning). Pain may be present in the presence of a normal clinical examination and normal nerve conduction studies, which are a measure of large fibre function (11). The involvement of large fibres may cause numbness, tingling and loss of protective sensation.

Neuropathic pain is frequently bothersome and often limits physical activity, quality of life and work productivity (3,11–13). Additionally, people with neuropathy utilize more health resources than those without (14). Foot ulceration, which depends on the degree of foot insensitivity (15), and amputation are important and costly sequelae of diabetic neuropathy (16).

Diabetic autonomic neuropathies (DAN) affect the autonomic neurons and may target the innervation of the heart (cardiac autonomic neuropathy [CAN]), gastrointestinal tract, genitourinary system, sexual function, pupillary responses and sweating. Specialized laboratories that study clinical autonomic disorders, including DAN, are available at some centres (17).

The prevalence of CAN increases with diabetes duration in people with type 1 and type 2 diabetes. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) study, prevalence rates of at least 30% were observed after 20 years of type 1 diabetes (2,18). CAN may be present in up to 60% of people with type 2 diabetes after 15 years (19). CAN may be identified by heart rate variability and has been shown to be a risk factor for mortality in diabetes (20–22); however, further study is required to determine if interventions are helpful in reducing the risk of subsequent cardiac events and mortality.

Other features of CAN are postural hypotension, and resting tachycardia (i.e. 100 beats/min). For postural hypotension, the diagnosis is made by measuring supine, followed by a 1-minute standing blood pressure (BP) and pulse. A fall of greater than 20 mmHg systolic

Conflict of interest statements can be found on page S219.

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without an appropriate increase in heart rate is significant. Treatment includes conservative measures to increase fluid and salt intake, caution with exacerbating medications, compression stockings and sleeping with the head of the bed elevated. Specific therapies include fludrocortisone, midodrine and droxidopa (approved in the United States but not Canada), with care taken to monitor for supine hypertension (10,23,24).

Gastrointestinal neuropathies may be associated with gastroparesis, constipation, diarrhea (especially nocturnal), and incontinence. A gastric emptying study may be helpful in diagnosis. Treatment approaches include dietary measures, withdrawal of exacerbating medications (e.g. glucagon-like peptide-1 [GLP-1] receptor agonists, opioids) and, in severe instances, temporary use of the prokinetic agent, metoclopramide, but its use is limited by risk of extrapyramidal side effects.

Bladder dysfunction in DAN includes loss of bladder sensation and later detrusor dysfunction with overflow incontinence, predisposition to infection and inability to empty. Bladder function should be evaluated in people with diabetes with recurrent urinary tract infections, pyelonephritis or incontinence. The use of amitriptyline is contraindicated in people with diabetic bladder involvement owing to potential anticholinergic side effects.

Erectile dysfunction in men is the most common symptom of DAN with a prevalence of up to 40% (25), although it may be associated with the presence or the absence of DSPN. Treatment includes phosphodiesterase-5 inhibitors for mild erectile dysfunction, local prostaglandin injections, vacuum devices or prostheses (see Sexual Dysfunction and Hypogonadism in Men with Diabetes chapter, p. S228).

Sudomotor abnormalities are loss of sweating in the extremities with inappropriate truncal sweating, dry skin or heat intolerance. Gustatory sweating may occur and consists of excessive sweating in the head and neck triggered by food consumption or the smell of food.

Mononeuropathies, or focal neuropathies, can occur with involvement of the median, ulnar, radial and common peroneal nerves. Carpal tunnel syndrome and ulnar neuropathy at the elbow is also common in diabetes and can be distinguished from polyneuropathy by electrophysiological studies (26).

There are other forms of diabetic-related neuropathy that are less common, such as diabetic radiculoplexus neuropathy (also known as diabetic amyotrophy or diabetic polyradiculoneuropathy), cranial neuropathies (primarily involving cranial nerves III, IV, VI, and VII), thoracic radiculopathy and others (27). Diabetes may also target other parts of the nervous system, including the brain (28).

The underdiagnosis of neuropathy is a fundamental problem in the primary care of people with diabetes and impedes the benefits of early identification, the management necessary to achieve improved glycemic control and the prevention of neuropathy-related sequelae (29). However, it is important to exclude other causes of neuropathy besides diabetes by way of obtaining a family and medication (including alcohol) history. Relevant investigations may include: serum B12 (particularly with use of metformin), folic acid, thyroid function, complete blood count, serum creatinine and protein electrophoresis.

Screening for Peripheral Neuropathy

Asymptomatic screening for neuropathy can be performed rapidly and reliably using the 10 g Semmes-Weinstein monofilament or the 128 Hz tuning fork over the dorsal aspect of the great toe bilaterally (30–34). Other screening tests can include pinprick or temperature (starting distally bilaterally and moving proximally until a sensory threshold is identified) and ankle reflexes. Methods for using the monofilament or tuning fork to detect diabetic neuropathy are outlined in Appendix 11A. Rapid Screening for Diabetic Neuropathy Using the 10 g Semmes-Weinstein Monofilament, and Appendix 11B. Rapid Screening for Diabetic Neuropathy Using the 128 Hz Vibration Tuning Fork (30,31,34). Additionally, several clinical scoring systems based on composite measures of symptoms and signs have been developed and evaluated for identification of neuropathy, but it is not clear if these more complex procedures have benefit over simplified screening tests for neuropathy identification. Evaluation for neuropathy in the lower limbs should also accompany the evaluation of vascular supply and skin integrity as outlined in the Foot Care chapter, p. S222. In addition, it is important to recognize that the 10 g monofilament test for annual DSPN screening is different than the testing used to identify a foot at high risk for ulceration in the context of recognized neuropathy. Testing to assess risk for foot ulceration generally requires testing of 3 sites on each foot (see Appendix 12: Monofilament Testing in the Diabetic Foot, p. S322).

Individuals with asymmetrical manifestations of neuropathy, greater motor than sensory impairments, or rapidly progressive symptoms or signs of neuropathy may have nondiabetic causes of neuropathy that may require more careful evaluation, and referral for additional neurological evaluation should be considered.

Management of Diabetic Neuropathy

Intensive glycemic control is effective for the primary prevention and secondary intervention of neuropathy in people with type 1 diabetes (3,6,35,36). In fact, the benefits of intensive insulin treatment persist for over a decade for the primary prevention of neuropathy (37). In those with type 2 diabetes, target BG levels are associated with a reduced frequency of neuropathy (5,12,38). No other clearly efficacious disease-modifying treatments are currently available. Multiple treatments are available for the management of neuropathic pain, and detailed evidence-based guidelines on the treatment of painful diabetic neuropathy (PDN) have been published (39). An important observation is that few people have complete relief of painful symptoms with any treatment, and that a 30% to 50% reduction in baseline pain, usually measured by a visual analogue scale of 0 to 10 out of 10 maximal pain intensity, is considered to be a clinically meaningful response.

There are insufficient comparative studies to recommend which oral medication should be used first line, although the primary use of opioids for PDN, despite clinical trial evidence for pain efficacy (40–44), is not recommended due to the potential for dependency, tolerance, dose escalation and diversion (39,45). Anticonvulsants (46–54) and antidepressants (55–64) are most commonly used as first-line therapy. Details are listed in Table 1. Pregabalin and duloxetine have received approval for the treatment of neuropathic pain in diabetes by Health Canada.

Other effective therapeutic options include topical nitrate sprays (65,66), topical capsaicin (67–70) and transcutaneous electrical nerve stimulation (71,72). However, effective treatment with capsaicin involves short-term pain that limits its acceptability and generalizability in clinical practice. The surgical release of distal lower limb nerves is not recommended due to lack of evidence supporting efficacy (73) and the possible complications of foot and ankle surgery in people with diabetes.

Dose ranges for painful neuropathic symptoms described in Table 1 are for adults and are taken from published trials; smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and hepatic dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

Table 1
Treatment options for the management of painful diabetic peripheral neuropathy

	Suggested starting dose	Suggested titration if tolerated	Suggested maximal tolerated dose	Estimated monthly cost for starting dose
Anticonvulsants				
Gabapentin† (46,74)	300 mg BID or qhs	May titrate slowly up to 600 mg po qid	3,600 mg/day	BID: $24.34 (60) QD: $18.32 (30)
Pregabalin (47–49,52,53,75)	75 mg BID	May titrate slowly up to 300 mg po bid	600 mg/day	$98.77 (60)
Valproate (50,51)	250 mg BID	May titrate slowly up to 500 mg po bid	1,500 mg/day	$12.37 (60)
Antidepressants				
Amitriptyline †(56,57,61,72)	10 mg QHS	May titrate slowly up to 100 mg po qhs	150 mg/day	$14.49 (30)
Duloxetine (60,64)	30 mg OD	May titrate to 60 mg po od	120 mg/day	$28.22 (30)
Venlafaxine† (62,63,75–79)	37.5 mg BID	May titrate slowly up to 150 mg po bid	300 mg/day	$23.16 (60)
Opioids*				
***Note:* Although the following agents have demonstrated efficacy for neuropathic pain, their use should be selective, after other options have failed to be effective, and clinicians must be aware of the risks of tolerance, abuse, dependency and addiction (45). The limited use of these agents should follow the principles of the *2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain* (54).**				
Tramadol (44)*	50 mg QID	May titrate slowly up to 50 mg po qid	400 mg/day	$100.45 (120)
Tapentadol ER (40)*	100 mg BID	May titrate slowly up to 250 mg po bid	250 mg po bid	$118.49 (60)
Dextromethorphan (42)*	100 mg QID	May titrate slowly up to 200 mg po qid	960 mg/day	requires compounding of the capsules
Morphine sustained release (74)*	15 mg BID	May titrate slowly up to 60 mg po bid	180 mg/day	$27.61 (60)
Oxycodone ER (43)*	10 mg BID	May titrate slowly up to 40 mg po bid	160 mg/day	$42.60 (60)
Others				
Topical nitrate sprays (65,66,70)	30 mg spray to legs QHS	May titrate slowly up to 30 mg spray to legs bid	60 mg/day	
Capsaicin cream (68,69)**	0.075% cream applied 3–4 times per day	May titrate to 5–6 times per day	5–6 applications per day	$17.99
Transcutaneous electrical nerve stimulation	-	-	-	-

BID, 2 times a day; *OD*, once daily; *QHS*, every bedtime; *QID*, 4 times a day.
Dose ranges are for adults and are taken from published trials—smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and liver dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.
* Use with caution due to risks of dependency and tolerance; not advised as first-line therapy, and generally considered a treatment of last resort for painful neuropathy.
† Denotes that this drug is not currently approved by Health Canada for the management of neuropathic pain associated with diabetic peripheral neuropathy.

RECOMMENDATIONS

1. In people with type 2 diabetes, screening for peripheral neuropathy should begin at diagnosis of diabetes and occur annually thereafter [Grade D, Consensus]. In people with type 1 diabetes, annual screening should commence after 5 years' post-pubertal duration of diabetes [Grade D, Consensus].

2. Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10 g monofilament or loss of sensitivity to vibration at the dorsum of the great toe [Grade A, Level 1 (31,34)] (see Appendices 11A and 11B. Rapid Screening for Diabetic Neuropathy).

3. People with diabetes should be treated with intensified glycemic control to prevent the onset and progression of neuropathy [Grade A, Level 1A (3,35) for type 1 diabetes; Grade B, Level 2 (38) for type 2 diabetes].

4. The following agents may be used alone or in combination for relief of painful peripheral neuropathy:
   a. Anticonvulsants (pregabalin [Grade A, Level 1 (47,52)], gabapentin† [Grade B, Level 2 (46,74)], valproate† [Grade B, Level 2 (50,51)]
   b. Antidepressants (amitriptyline†, duloxetine, venlafaxine†) [Grade B, Level 2 (56,57,60,61,63,75)]
   c. Topical nitrate spray† [Grade B, Level 2 (65,66,70)]
   d. In people not responsive to the above agents, opioid analgesics (tramadol, tapentadol ER, oxycodone ER) may be used [Grade B, Level 2 (41,43,44)]. Prescribers should be cautious due to risks of abuse, dependency and tolerance, and follow the recommendations of the *2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain* (54) [Grade D, Consensus].

Footnote:
†Denotes that this drug is not currently approved by Health Canada for the management of neuropathic pain associated specifically with diabetic peripheral neuropathy.
Most studies failed to achieve Grade A, Level 1 due to a <80% completion rate (39).

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *BMI*, body mass index; *CAD*, cardiac autonomic neuropathy; *DAN*, diabetic autonomic neuropathy; *DPN*, diabetic peripheral neuropathy; *PDN*, painful diabetic neuropathy.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Foot Care, p. S222
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247

Relevant Appendices

Appendix 11A. Rapid Screening for Diabetic Neuropathy Using the 10 g Semmes-Weinstein Monofilament
Appendix 11B. Rapid Screening for Diabetic Neuropathy Using the 128 Hz Vibration Tuning Fork
Appendix 12. Monofilament Testing in the Diabetic Foot

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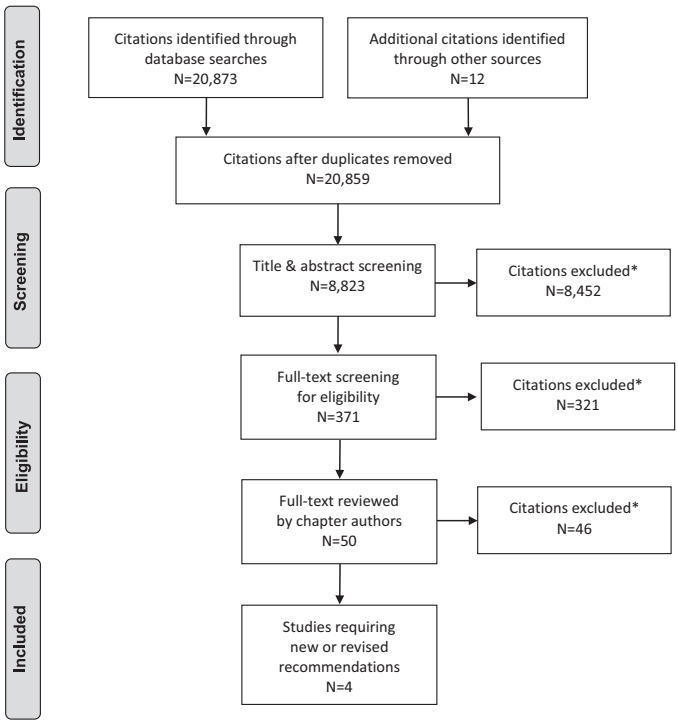
Literature Review Flow Diagram for Chapter 31: Neuropathy



*Excluded based on: population, intervention/exposure, comparator/control or study design

From reference 80.

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2018 Clinical Practice Guidelines

Foot Care

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Lower extremity complications are a major cause of morbidity and mortality in people with diabetes.
- The treatment of foot ulcers in people who have diabetes requires an interprofessional approach that addresses glycemic control, infection, offloading of high-pressure areas, lower-extremity vascular status and local wound care.
- Antibiotic therapy is not required for uninfected neuropathic foot ulcers.
- Proprietary adjunctive wound dressings and technologies, including antimicrobial dressings, lack sufficient evidence to support routine use in the treatment of neuropathic ulcers.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Diabetes can cause nerve damage (also known as "diabetic peripheral neuropathy") and poor blood flow or circulation to the legs and feet (also known as "peripheral arterial disease").
- As a result, people with diabetes are less likely to feel a foot injury, such as a blister or cut. Diabetes can make these injuries more difficult to heal. Unnoticed and untreated, even small foot injuries can quickly become infected, potentially leading to serious complications.
- A good daily foot care routine may help keep your feet healthy:
  - Examine your feet and legs daily
  - Care for your nails regularly
  - Apply moisturizing lotion if your feet are dry (but not between the toes)
  - Wear properly fitting footwear
  - Test your bath water with your hand before you step in, to make sure the water is not too hot
- If you have any corns (thick or hard skin on toes), calluses (thick skin on bottom of feet), ingrown toenails, warts, splinters or other wounds, have them treated by your doctor or other foot care specialist (such as a foot care nurse, podiatrist or chiropodist). Do not try to treat them yourself.
- If you have any swelling, warmth, redness or pain in your legs or feet, see your health-care provider or foot specialist right away.

Introduction

Foot complications are a major cause of morbidity and mortality in people who have diabetes, and contribute to increased health care use and costs (1–7). People with diabetes who have peripheral neuropathy and peripheral arterial disease are at risk of developing foot ulcers and infection that may lead to lower-extremity amputation (8–11). The frequency of amputation is much higher in people with diabetes than people without diabetes (12,13). This is especially true in developed nations, such as Canada, where adults with diabetes have 20-fold greater likelihood of being hospitalized for nontraumatic lower limb amputation than adults without diabetes (14). In the United States, the frequency of lower-extremity amputation decreased by 28.8% from 2000 to 2010, but the use of other orthopedic treatments for diabetic foot ulcers increased by 143% during this period (15). Preventive measures, foot care education, and early and aggressive treatment of diabetic foot problems are important components of diabetes care.

Risk Assessment

Risk factors for developing foot ulcers in people with diabetes include peripheral neuropathy, previous ulcer or amputation, structural deformity, limited joint mobility, peripheral arterial disease, microvascular complications, increased levels of glycated hemoglobin (A1C) and onychomycosis (16,17). Loss of sensation to the 10 g Semmes-Weinstein monofilament at the plantar surface of the foot is a significant and independent predictor of future foot ulcer and lower-extremity amputation (18–20).

Several wound classifications have been developed to provide objective assessment of foot ulcer severity. The simple Wagner classification is used commonly: Wagner Grade 0, skin intact; Grade 1, superficial ulcer; Grade 2, ulcer extending to tendon, capsule or bone; Grade 3, deep ulcer with osteomyelitis or abscess; Grade 4, gangrene of toes or forefoot; Grade 5, gangrene of midfoot or hindfoot. The University of Texas Diabetic Wound Classification System has been validated as a predictor of serious outcomes in people with diabetes who have foot ulcers (21,22) (Table 1).

In people who have ischemia, the distribution of peripheral arterial disease is greater in the arterial tree below the knee in people with diabetes compared with people without diabetes (23). Noninvasive assessments for peripheral arterial disease in people with diabetes include the blood pressure (BP) ankle-brachial index (ratio of ankle to brachial systolic BP), systolic toe pressure by photoplethysmography, transcutaneous oximetry and Doppler arterial flow studies (24,25). Although the ankle-brachial index in some clinical settings is a readily available and easy-to-perform technique, it may underestimate the degree of peripheral arterial

Conflict of interest statements can be found on page S225.

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Table 1
University of Texas Diabetic Wound Classification System*

Stage	Grade			
	0	I	II	III
A (no infection or ischemia)	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

* Adapted from reference 21.

Table 2
Key elements of the lower extremity physical examination*

Element	Parameter
Inspection	• Gait • Foot morphology (Charcot arthropathy, bony prominences) • Toe morphology (clawtoe, hammertoe, number of toes) • Skin: blisters, abrasions, calluses, subkeratotic hematomas or hemorrhage, ulcers, absence of hair, toe nail problems, edema, abnormal color • Status of nails • Foot hygiene (cleanliness, tinea pedis)
Palpation	• Pedal pulses • Temperature (increased or decreased warmth)
Protective sensation	• Sensation to 10 g monofilament**
Footwear	• Exterior: signs of wear, penetrating objects • Interior: signs of wear, orthotics, foreign bodies

* Adapted from references 19 and 38 to 43.
** See Appendix 12. Monofilament Testing in the Diabetic Foot.

obstruction because of medial arterial wall calcification in lower-extremity arteries (26,27). Photoplethysmography assesses the intensity of light reflected from the skin surface and red blood cells, which is indicative of arteriolar pulse flow; measurement of systolic toe pressure by photoplethysmography may be more accurate than ankle-brachial index in determining the presence of arterial disease in people with diabetes (28).

It is important to recognize the potential limitations inherent with noninvasive diagnostic tests for peripheral arterial disease (29,30). Other studies that are available for the evaluation of lower-limb ischemia that do not require arterial access include intra-arterial digital subtraction contrast arteriography, magnetic resonance angiography and computed tomographic angiography, but these studies may be complicated by contrast-induced renal failure or gadolinium-associated nephrogenic systemic fibrosis (31–35). Consultation with a specialist in vascular medicine or surgery should be undertaken as soon as possible for people who have suspected lower extremity ischemia (30,36).

The foot examination is important and should include footwear assessment (19,37,38) (Table 2). Assessment of skin temperature is important because increased warmth may indicate the presence of inflammation or acute Charcot neuroarthropathy in a foot that has lost protective sensation (39–41). In addition, erythema and swelling may be indicators of cellulitis or Charcot neuroarthropathy (42,43). The clinical and radiographic differentiation between acute Charcot foot and infection may be difficult (44). Plain radiographs have low sensitivity and specificity in differentiating osteomyelitis from Charcot changes. Magnetic resonance imaging (MRI) of the foot may help clarify this differential diagnosis, but no diagnostic imaging studies are definitive, and the results of all imaging studies must be interpreted carefully and correlated with the clinical presentation (45,46).

Preventive Care and Treatment

Preventive measures against the risk of amputation include regular foot examination, evaluation of amputation risk, regular callus debridement, patient education, professionally fitted therapeutic footwear to reduce plantar pressure and accommodate foot deformities, and early detection and treatment of diabetic foot ulcers (47,48). Many studies that have assessed interventions to prevent and treat diabetic foot ulcers have had limited quality of supportive evidence because of problems in study design and methods (49,50). However, the treatment of foot ulcers typically is most effective with an interprofessional approach and includes measures to improve glycemic control, decrease mechanical pressure with off-loading, treat infection, ensure adequate lower-extremity arterial inflow and provide local wound care (51–55).

Specific recommendations about wound dressing types cannot be made for typical diabetic foot ulcers because there is insufficient evidence to support any type of dressing over another (56–60). The essentials of good wound care include maintaining an optimal wound environment, off-loading pressure from the ulcer and regular debridement of nonviable tissue (58,61,62); wound dressings that maintain a physiologically moist wound environment should be selected. There are insufficient data to support the use of specific dressing types or antimicrobial dressings in the routine treatment of diabetic foot wounds (48,51–59). There is also insufficient evidence to make any recommendation about the role of suction wound dressings (referred to as “negative pressure wound therapy”) in the routine treatment of neuropathic wounds, but there is some evidence in favour of suction wound dressings for more advanced diabetic foot ulcers or after extensive debridement (58,61,63–66). Other adjunctive measures for wound healing, such as topical growth factors and dermal substitutes, have been evaluated for the treatment of diabetic foot ulcers, but the studies have been limited in sample size, duration and follow up, and the results are not sufficiently conclusive to support the use of these therapies (57,58,67–70).

Pressure off-loading may be achieved with temporary footwear until the ulcer heals and the tissues of the foot stabilize. Removable and nonremovable walker boots and total contact casts are effective in decreasing pressure at plantar surface ulcers (71–76). Although total contact casts are effective in supporting the healing of noninfected, nonischemic plantar surface neuropathic ulcers, total contact casting requires careful patient selection and personnel who have specialized training to minimize the risk of developing iatrogenic complications (74,75,77–79). When bony foot deformity prevents the fitting of appropriate footwear or off-loading of pressure-related ulcers, consultation with a surgeon skilled in foot surgery may be considered to evaluate and treat the deformity (80–82).

Treatment of the acute Charcot foot requires immobilization of the foot, typically for several months, in a total contact cast, removable walker boot or custom orthosis until consolidation occurs (63). Surgical stabilization may be indicated for Charcot arthropathy associated with marked instability, deformity or nonhealing ulcers.

Table 3
Empiric antimicrobial therapy for infection in the diabetic foot*

Infection Severity	Antimicrobial Agent†,‡,§
Localized infections: Neither limb nor life threatening Usually associated with cellulitis surrounding an ulcer Purulent debris may be present at the base of the ulcer Usual organisms: aerobic gram-positive cocci (*S. aureus* and β-hemolytic streptococci) Frequently treated with outpatient oral antimicrobial therapy	• Cloxacillin • Amoxicillin-clavulanic acid • Cephalexin • SMX-TMP • Clindamycin • Doxycycline
More extensive infections: • Includes more severe infections, including more extensive cellulitis, plantar abscess and deep space infections • The choice of oral or parenteral should be guided by the extent of the infection and the patient's overall clinical status • Initial antimicrobial therapy against staphylococci, streptococci, anaerobes and common *Enterobacteriaceae* species • Empiric treatment targeting *P. aeruginosa* is generally unnecessary unless risk factors present (e.g. history of foot soaking, severe or chronic infection) • Patients who are not toxic may be treated with debridement and oral antimicrobial therapy • Patients who are ill or toxic despite moderate local signs are treated as having a severe infection: ◦ Limb or life threatening ◦ Frequently polymicrobial ◦ Immediate hospitalization, early surgical debridement and parenteral antimicrobial therapy ◦ If MRSA is present or suspected, consider adding vancomycin, linezolid or daptomycin	**Oral Options** • SMX-TMP plus metronidazole or clindamycin • Ciprofloxacin or levofloxacin plus clindamycin or metronidazole • Amoxicillin-clavulanic acid • Moxifloxacin • Linezolid **Parenteral Options** • Cefoxitin • 1st, 2nd or 3rd generation cephalosporin plus metronidazole • Piperacillin-tazobactam • Clindamycin plus 3rd generation cephalosporin • Carbapenem
Osteomyelitis: • Treat with intravenous therapy or long-term oral antimicrobial therapy using agents that are well absorbed from the gastrointestinal tract and have good distribution to bone and tissue • Surgical debridement indicated to remove necrotic debris, abscess or sequestrum • Therapy should be based on culture results whenever possible • If MRSA is present or suspected, consider adding vancomycin, linezolid or daptomycin	**Oral Options** • Cloxacillin • Cephalexin • SMX-TMP • Clindamycin • Amoxicillin-clavulanic acid • Linezolid • Doxycycline • SMX-TMP plus metronidazole or clindamycin • Levofloxacin or ciprofloxacin plus metronidazole or clindamycin **Parenteral Options** • Piperacillin-tazobactam • Clindamycin po/iv plus 3rd generation cephalosporin • Carbapenem

* Modified and used with permission from reference 90.
MRSA, methicillin-resistant *Staphylococcus aureus*; *SMX-TMP*, sulfamethoxazole-trimethoprim.
† The agents suggested in this section are for empiric therapy prior to the availability of final culture and susceptibility results. Knowledge of local epidemiology and antimicrobial resistance profiles must also guide therapeutic choices.
‡ Many of the agents identified in this table do not have Health Canada approval specifically for treatment of diabetic foot infections, including osteomyelitis, but may have an indication for the treatment of skin and soft tissue infections or antimicrobial activity against typical pathogens encountered in osteomyelitis of the diabetic foot.
§ Duration of therapy is based on clinical response. However, typical treatment courses for skin and soft tissue infections range from 7 (mild) to 21 (severe) days, and the treatment of osteomyelitis may require 4 to 6 weeks of parenteral or several months of oral antimicrobial therapy. Whenever possible, it is desirable to switch to oral antimicrobial therapy to avoid complications from parenteral administration.

Although bisphosphonates have been considered for the treatment of Charcot arthropathy, further studies are necessary to fully evaluate these agents and other medical therapies in the routine treatment of Charcot arthropathy (83–89).

Infection may complicate foot ulcers and may progress rapidly to become limb and/or life threatening (90). When infections begin, the most frequent pathogens typically include *Staphylococcus aureus, Streptococcus pyogenes* (group A streptococcus) and *Streptococcus agalactiae* (group B streptococcus). With persistent infection and the presence of devitalized tissue, gram-negative and anaerobic pathogens may cause polymicrobial infection (36,91). Specimens for culture from the surface of wounds are unreliable, and specimens from deeper tissues obtained by debridement are more likely to determine the correct bacterial pathogens for antimicrobial therapy (92–96). Initial therapy typically includes empiric, broad-spectrum antibiotics, and subsequent antibiotic selection is tailored to the sensitivity results of cultured specimens. With the exception of a few antimicrobial agents that have a specific indication for the treatment of diabetic foot infections, most agents available for use are selected for their antibacterial spectrum (36,95–97). Guidelines are available for antimicrobial choices in the empiric treatment of diabetic foot infections (Table 3) (98).

Achieving target glycemic control may be associated with decreased amputation frequency (99). Poor glycemic control may be associated with immunopathy and blunted cellular response to infection. Many people (50%) who have diabetes and a major limb infection may not have fever or leukocytosis at presentation (100). Deep infections require prompt surgical debridement and appropriate antibiotic therapy (36,101).

In medically suitable individuals who have peripheral arterial disease and a history of ulceration or amputation, distal limb revascularization may improve long-term limb salvage. Endovascular techniques with angioplasty and stenting for infrainguinal arteries may be effective to achieve limb salvage, but the long-term success is less in people with diabetes than people without diabetes (83,102). A specific evidence-based recommendation about the type of revascularization technique cannot be made, and the preferred method is based on the judgment of the vascular surgeon, in consideration of medical and surgical risks (29,30).

There is limited evidence to confirm an added benefit of hyperbaric oxygen therapy in reducing the indication for amputation or improving wound healing in individuals with diabetes. Therefore, hyperbaric oxygen therapy is not recommended for the routine treatment of infected or noninfected neuropathic or ischemic foot ulcers.

RECOMMENDATIONS

1. Health-care providers should perform foot examinations to identify people with diabetes at risk for ulcers and lower-extremity amputation [Grade C, Level 3 (9,18)] at least annually and at more frequent intervals in high-risk people [Grade D, Level 4 (1)]. The examination should include assessment for neuropathy, skin changes (e.g. calluses, ulcers, infection), peripheral arterial disease (e.g. pedal pulses and skin temperature) and structural abnormalities (e.g. range of motion of ankles and toe joints, bony deformities) [Grade D, Level 4 (1)].

2. People with diabetes who are at high risk of developing foot ulcers should receive foot care education (including counseling to avoid foot trauma) and professionally fitted footwear [Grade D, Consensus]. When foot complications occur, early referral to a health-care professional trained in foot care is recommended [Grade C, Level 3 (37,48,49)].

3. People with diabetes who develop a foot ulcer or show signs of infection even in the absence of pain should be treated promptly by an interprofessional health-care team when available with expertise in the treatment of foot ulcers to prevent recurrent foot ulcers and amputation [Grade C, Level 3 (52)].

4. There is insufficient evidence to recommend any specific dressing type for typical diabetic foot ulcers [Grade C, Level 3 (103)]. Debridement of nonviable tissue [Grade A, Level 1A (104)] and general principles of wound care include the provision of a physiologically moist wound environment, and off-loading the ulcer [Grade D, Consensus].

5. There is insufficient evidence to recommend the routine use of adjunctive wound-healing therapies (e.g. topical growth factors, granulocyte colony-stimulating factors or dermal substitutes) for typical diabetic foot ulcers. Provided that all other modifiable factors (e.g. pressure off-loading, infection, foot deformity) have been addressed, adjunctive wound-healing therapies may be considered for nonhealing, nonischemic wounds [Grade A, Level 1 (69,70)].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose, *BP*, blood pressure; *MRI;* magnetic resonance imaging.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Neuropathy, p. S217

Relevant Appendices

Appendix 12. Monofilament Testing in the Diabetic Foot
Appendix 13. Diabetes and Foot Care: A Checklist
Appendix 14. Diabetic Foot Ulcers—Essentials of Management

Author Disclosures

No authors have anything to disclose.

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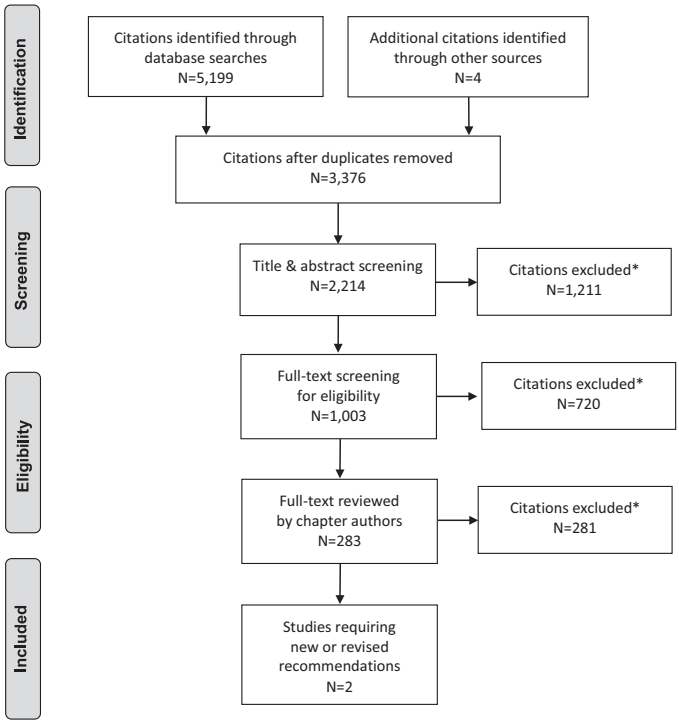
Literature Review Flow Diagram for Chapter 32: Foot Care



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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2018 Clinical Practice Guidelines

Sexual Dysfunction and Hypogonadism in Men With Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

Richard Bebb MD, ABIM, FRCPC, Adam Millar MD, MScCH, FRCPC, Gerald Brock MD, FRCSC

KEY MESSAGES REGARDING SEXUAL DYSFUNCTION IN MEN WITH DIABETES

- Erectile dysfunction affects approximately 34% to 45% of adult men with diabetes. It has been demonstrated to negatively impact quality of life among those affected across all age strata and may be an early clinical indication of cardiovascular disease.
- All adult men with diabetes should be regularly screened for erectile dysfunction with a sexual function history.
- The current mainstay of therapy for erectile dysfunction is phosphodiesterase type 5 inhibitors. They have been shown to have major impacts on erectile function and quality of life, with a low reported side effect profile, and should be offered as first-line therapy to men with diabetes wishing treatment for erectile dysfunction.

KEY MESSAGES REGARDING HYPOGONADISM IN MEN WITH DIABETES

- Hypogonadotropic hypogonadism is common in men with type 2 diabetes, with a prevalence of up to 40%.
- Hypogonadal men with diabetes have a higher risk for cardiovascular mortality than eugonadal men with diabetes.
- Screening for symptomatic hypogonadism in men with type 2 diabetes is recommended.
- Evidence is conflicted as to whether treatment of hypogonadism in men with diabetes can increase quality of life, improve body composition, weight loss and glycemic control.
- Observational studies assessing the impact of testosterone use on cardiovascular health in hypogonadal men have produced mixed results. Randomized, placebo-controlled studies have been too small or short in duration to adequately answer this question.

KEY MESSAGES FOR MEN WITH DIABETES

- Low testosterone is common in men with type 2 diabetes.
- Symptoms of low testosterone can include: diminished interest in sex, erectile dysfunction, reduced lean body mass, depressed mood and lack of energy.
- If you are experiencing symptoms of low testosterone, you should talk with your health-care provider.

Erectile Dysfunction

Erectile dysfunction (ED) affects approximately 34% to 45% of men with diabetes and has been demonstrated to negatively impact quality of life among those affected across all age strata (1), with a greater impact on those with permanent—rather than intermittent—ED (2,3). Recent reports describe up to one-third of newly diagnosed men with diabetes have ED at presentation (4), with upward of 50% of men 6 years after diagnosis (5,6). In addition, studies indicate that 40% of men with diabetes greater than 60 years of age have complete ED (7–15).

Recent studies have reported that alteration of the cyclic guanosine monophosphate (cGMP)/nitric oxide (NO) pathway among men with diabetes with impaired vascular relaxation is related to endothelial dysfunction (16–18). Among men with diabetes, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen-deficiency states (19) and cardiovascular disease (CVD) (6,11,12,20–24).

ED as a marker of potential cardiovascular (CV) events has been reported by numerous investigators (25–34). In fact, ED has been shown to be significantly associated with all-cause mortality and CV events (35–37). Diabetic retinopathy has been shown to correlate with the presence of ED (11,13,38). Organic causes of ED include microvascular and CV disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED. In spite of the overwhelming amount of data linking ED and diabetes, it is often neglected by clinicians treating men with diabetes (39).

Compared with the general population, multiple studies have reported that men with diabetes have higher rates of hypogonadism (19,40–44). One report described a correlation between glycemic control and testosterone levels (45). Importantly, phosphodiesterase type 5 (PDE5) inhibitors appear to be less effective in men with diabetes with hypogonadism (41,43,46,47). In this population, treatment of nonresponders to PDE5 inhibitors with testosterone replacement is successful in roughly 50% of individuals. In addition, ED is a side effect of many drugs commonly prescribed to men with diabetes, such as certain antihypertensives and antidepressants. Obstructive sleep apnea (OSA) is commonly associated with ED and, like diabetes, is an independent risk factor for the presence of ED (48). Screening for OSA in men with obesity with type 2 diabetes and ED should be considered.

Conflict of interest statements can be found on page S231.

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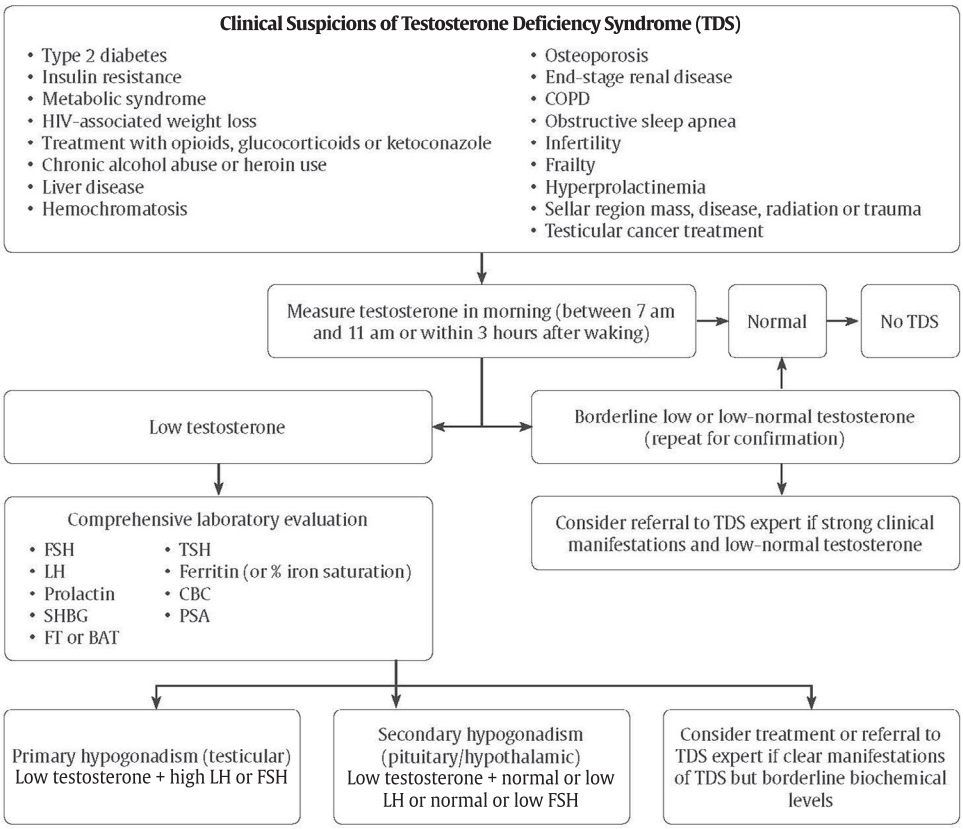

Figure 1. Diagnostic workup of hypogonadism (TDS) (modified from reference [91]).
BAT, calculated bioavailable testosterone; *CBC*, complete blood count; *COPD*; chronic obstructive pulmonary disease; *FT*, free testosterone; *FSH*, follicle stimulating hormone; *LH*, luteinizing hormone; *PSA*, prostate specific antigen; *SHBG*, sex hormone-binding globulin; *TSH*, thyroid stimulating hormone.

Screening for Erectile Dysfunction

All adult men with diabetes should be regularly screened for ED with a sexual function history. Screening for ED in men with type 2 diabetes should begin at diagnosis of diabetes. Validated questionnaires (e.g. International Index of Erectile Function (49,50) or Sexual Health Inventory for Men) (51) have been shown to be both sensitive and specific in determining the presence of ED and providing a means of assessing response to therapy (24). Men with diabetes and ED should be further investigated for hypogonadism (Figure 1).

Treatment of ED

While no randomized clinical trials have demonstrated that interventions that improve glycemic control also reduce the incidence and progression of ED, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glycemic control was effective for primary prevention of and secondary intervention for neuropathy, a condition that can impair sensory feedback from the penis, leading to reduced erectile function (52–54). The current data are controversial as they relate to diet, glycemic control and ED, with both positive and negative studies (36,55–57). Based on these conflicting data, a prudent clinician should encourage optimal glycemic control as a potential factor in maintaining erectile function (36,58,59).

Dyslipidemia and hypertension are also risk factors for ED. A meta-analysis of statin use in older men, many of whom had diabetes, suggests a benefit from statin treatment on erectile function. Diabetes-specific data are lacking (60). A small study of losartan in combination with tadalafil in men with type 2 diabetes showed an improved ED response rate compared to tadalafil monotherapy (61).

The current mainstay of treatment for ED in men with diabetes is therapy with PDE5 inhibitors (62–64). They have been reported to have a major impact on erectile function and quality of life, and should be offered as first-line therapy to men with diabetes wishing treatment for ED (65–70) (see Figure 2). There is evidence that scheduled daily therapy is effective within the population with diabetes and ED (71,72), and may improve efficacy with lower rates of side effects, may reduce lower urinary tract symptoms and has the potential for endothelial benefits (73). Additionally, among PDE5 inhibitor failure patients, use of a vacuum constriction device may salvage a significant percentage of men with erectile function and should be considered (74,75).

Contraindications for the use of PDE5 inhibitors include unstable angina or untreated cardiac ischemia and concomitant use of nitrates (5,76,77). Interestingly, men with diabetes appear to have lower rates of side effects with PDE5 inhibitors than the general population. This is believed to be a result of altered vasomotor tone or other factors (78).

Referral to a specialist in ED should be offered to men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated (see Figure 2). Second-line therapies (e.g. vacuum constriction devices [79], intracorporal injection therapy with prostaglandin E1 [PGE1] alone or in combination with papaverine and phentolamine [triple therapy], or intraurethral therapy using PGE1) or third-line therapy (penile prosthesis) may be considered for these men (80,81).

Ejaculatory Disorders

Ejaculatory disorders are a common disorder of sexual function in men with diabetes, occurring in 32%–67% of that population

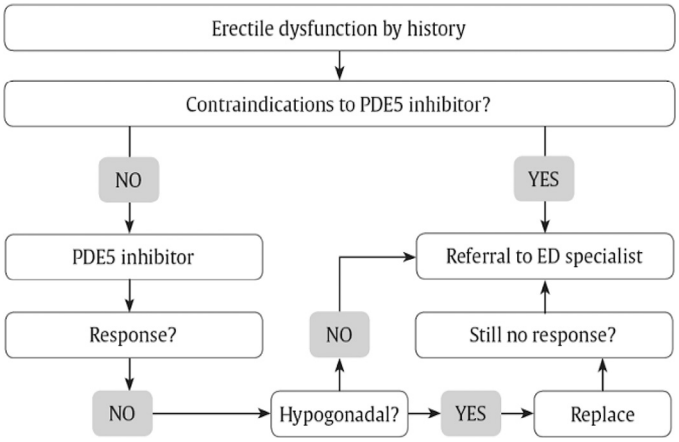

Figure 2. Management of erectile dysfunction in men with diabetes. *PDE5,* phosphodiesterase type 5.

(82,83). They range in scope from retrograde ejaculation, usually secondary to autonomic neuropathy with incomplete closure of the bladder neck during ejaculation, to premature or retarded ejaculation. Their recognition as an important component in sexual quality of life makes inquiry about ejaculatory function important.

Hypogonadism

Hypogonadotropic hypogonadism has a reported prevalence of 30% to 40% in men with type 2 diabetes (84–86). One study noted a prevalence of 30% in men with prediabetes, compared to 13.6% of age-matched controls (87). In contrast to type 2 diabetes, the prevalence of hypogonadism in men with type 1 diabetes is similar to the general male population (88,89). Although the pathophysiology may be related to numerous factors, including age, insulin resistance, glycemic control, concomitant sleep apnea and obesity, the most significant predictor is theorized to be the degree of central or visceral obesity (84,86,89,90). Insulin resistance is correlated with a reduction of sex hormone-binding globulin (SHBG). Measurement of total testosterone may be affected by low SHBG levels, giving the false impression of biochemical hypogonadism when bioavailable or free testosterone levels are still normal.

Biochemical testing should be by analysis of total testosterone levels drawn before 11 am or within 3 hours of awakening (91). Due to the natural variability of serum testosterone levels, repeat testing is often helpful to clarify the diagnosis. In men with diabetes with symptoms of hypogonadism but with total testosterone levels still in the lower normal range, measurement of bioavailable testosterone may be helpful.

Common symptoms of hypogonadism include fatigue, muscle weakness or muscle cramps, loss of sleep-related erections, low libido, night sweats or mood changes, such as depressive affect or irritability. A recent systematic review of male hypogonadism provides a more detailed discussion regarding diagnosis and treatment of testosterone deficiency (91).

Many men with type 2 diabetes and hypogonadism are asymptomatic, and treatment should be reserved for those who are biochemically hypogonadal and symptomatic. Some causes of secondary hypogonadism are potentially reversible, such as sleep apnea and obesity. Significant weight reduction is generally associated with an increase in testosterone in hypogonadal men with diabetes (92,93). In some instances, this can restore the eugonadal state without the need for testosterone replacement (92,93).

Conflicting evidence suggests that testosterone therapy in hypogonadal men with type 2 diabetes may increase quality of life or improve sexual function (44,94–98). Studies assessing whether testosterone treatment in hypogonadal men with diabetes can reduce glycated hemoglobin (A1C) values have also produced mixed results (93,94,99–104). A nonrandomized, ongoing, observational study of testosterone-treated men with hypogonadism with (40%) or without diabetes showed reductions in weight, visceral obesity, abdominal circumference, as well as decreased hypertension and insulin resistance over a 5-year study interval (105,106).

Hypogonadism has been associated both with risk factors of CVD, including carotid intimal medial changes in men with type 2 diabetes (107), and an increased risk of myocardial infarction (MI) and increased CV mortality (108,109). A 3-year randomized, placebo-controlled study of testosterone use in men with hypogonadism age 60 years or older showed no significant change in either carotid artery intimal medial thickness or coronary artery calcium scores. However, only 15% of this cohort had diabetes (110). Hypogonadism also predicted an increased CV risk in men (27% of whom had type 2 diabetes) with known coronary artery disease (CAD) (111). Several nonrandomized, observational studies have produced conflicting results in regards to cardiac risk vs. benefit from testosterone replacement (101,109,112).

As men with type 2 diabetes are high risk for CV events, any positive or negative impact could, therefore, potentially have a very significant clinical impact due to the high CVD event rate in this population. Until future studies clarify the effect of testosterone on CVD, it is prudent to discuss the issue with men with diabetes prior to initiating testosterone treatment.

To date, no large, randomized, placebo-controlled study has shown an increased risk of prostate cancer in men treated with testosterone. Monitoring for prostate cancer both prior to initiation of testosterone therapy and while on therapy is recommended.

Evaluation of hypogonadal symptoms

Biochemical testing is recommended in men with diabetes who are symptomatic. In the absence of symptoms of hypogonadism, biochemical testing is not indicated. OSA is very common in people with type 2 diabetes and obesity (113). Increasing age and obesity are risk factors (113). When hypogonadotrophic hypogonadism is diagnosed in men with type 2 diabetes, the presence of underlying OSA should be considered.

Treatment of hypogonadism

There is no evidence that 1 preparation of testosterone is superior to another in the relief of hypogonadal symptoms or the prevention of hypogonadism-related complications. The selection of a testosterone preparation should consider the benefits and risks of testosterone therapy in addition to patient preference. Monitoring the effects of testosterone should be done in accordance with national guidelines, such as those recommended by the Endocrine Society or the *Diagnosis and management of testosterone deficiency syndrome in men: Clinical Practice Guideline* (91).

RECOMMENDATIONS

1. All adult men with diabetes should be regularly screened for ED with a sexual function history [Grade D, Consensus].
2. A PDE5 inhibitor should be offered as first-line therapy to men with diabetes and ED in either an on-demand [Grade A, Level 1A (65–71)] or daily-use [Grade B, Level 2 (71,72)] dosing regimen.
3. Men with diabetes and ED who do not respond to PDE5 inhibitors should be investigated for hypogonadism with measurement of a morning serum total testosterone level drawn before 11 am [Grade D, Level 4 (19,40,41,43)].

4. Referral to a specialist in ED should be considered for eugonadal men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated [Grade D, Consensus].

5. Men with diabetes and ejaculatory dysfunction who are interested in fertility should be referred to a health-care professional experienced in the treatment of ejaculatory dysfunction [Grade D, Consensus].

Abbreviations:
A1C, glycated hemoglobin; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CAD*, coronary artery disease; *ED*, erectile dysfunction; *NO*, nitrous oxide; *PDE5*, phosphodiesterase type 5; *OSA*, obstructive sleep apnea; *SHBG*, sex hormone-binding globulin.

Other Relevant Guidelines

Cardiovascular Protection in People With Diabetes, p. S162
Screening for the Presence of Cardiovascular Disease, p. S170
Diabetes in Older People, p. S283

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Dr. Brock reports personal fees from Lilly, Pfizer, Astellas, Ferring, Boston Scientific, and Paladin, outside the submitted work. No other author has anything to disclose.

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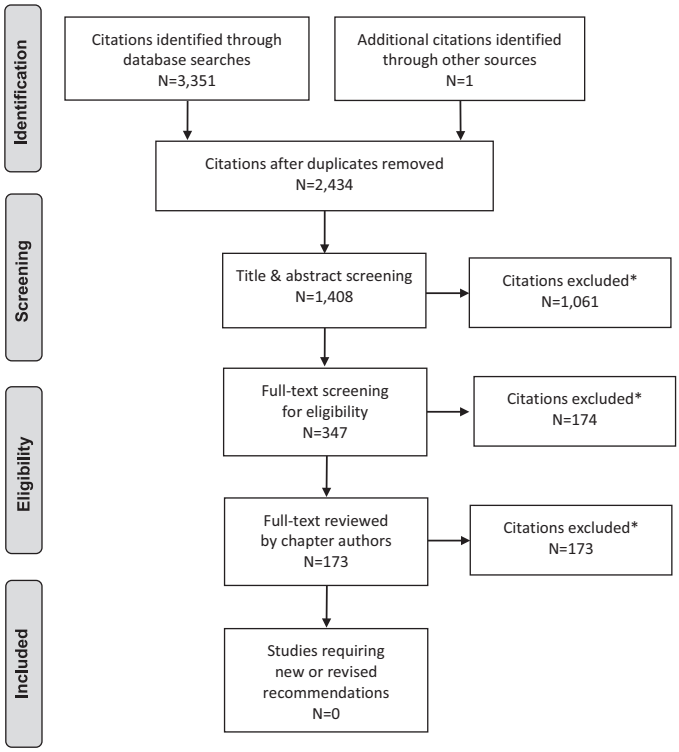
Literature Review Flow Diagram for Chapter 33: Sexual Dysfunction and Hypogonadism in Men with Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (114).

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2018 Clinical Practice Guidelines

Type 1 Diabetes in Children and Adolescents

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Suspicion of diabetes in a child should lead to immediate confirmation of the diagnosis and initiation of treatment to reduce the likelihood of diabetic ketoacidosis.
- Management of pediatric diabetic ketoacidosis differs from diabetic ketoacidosis in adults because of the increased risk for cerebral edema. Pediatric protocols should be used.
- Children should be referred for diabetes education, ongoing care and psychosocial support to a diabetes team with pediatric expertise.

KEY MESSAGES FOR PEOPLE WITH CHILDREN AND ADOLESCENTS WITH DIABETES

- When a child is diagnosed with type 1 diabetes, the role of a caregiver becomes more important than ever. Family life and daily routines may seem more complicated in the beginning but, over time, and with the support of a diabetes team, these improve. Families discover that a child can have a healthy and fulfilling life with diabetes.

Note: Unless otherwise specified, the term "child" or "children" is used for individuals 0 to 18 years of age, and the term "adolescent" for those 13 to 18 years of age.

Introduction

Diabetes mellitus is the most common endocrine disease and one of the most common chronic conditions in children. Type 2 diabetes and other types of diabetes, including genetic defects of beta cell function, such as monogenic and neonatal diabetes, are being increasingly recognized in children and should be considered when clinical presentation is atypical for type 1 diabetes (for additional details see Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10). This section addresses those areas of type 1 diabetes management that are specific to children.

Education

Children with new-onset type 1 diabetes and their families require intensive diabetes education by an interprofessional pediatric diabetes health-care (DHC) team that should include either a pediatric endocrinologist or pediatrician with diabetes expertise, dietician, diabetes nurse educator, social worker and mental health professional to provide them with the necessary skills and knowledge to manage this disease. The complex physical, developmental and emotional needs of children and their families necessitate specialized care to ensure the best long-term outcomes (1,2). Education topics must include insulin action, administration and dosage adjustment; blood glucose (BG) and ketone monitoring; sick-day management and prevention of diabetic ketoacidosis (DKA); nutrition therapy; physical activity; and prevention, detection and treatment of hypoglycemia.

Anticipatory guidance and healthy behaviour counselling should be part of routine care, especially during critical developmental transitions (e.g. daycare, school entry, adolescence). Health-care providers should regularly initiate discussions with children and their families about school, diabetes camp, psychological issues, fear of hypoglycemia, substance use, obtaining a driver's license and career choices. Behavioural interventions that have been applied broadly to clinic-based populations with a focus on improving self-efficacy and self-management skills have shown little benefit on improving glycemic control, but may improve caregiver coping skills and reduce parent-child conflict, emphasizing the need for a continuing programme of education (3–5).

Children with new-onset diabetes who present with DKA require a short period of hospitalization to stabilize the associated metabolic derangements and to initiate insulin therapy. Outpatient education for children with new-onset diabetes has been shown to be less expensive than inpatient education and associated with similar or slightly better outcomes when appropriate interprofessional resources to provide outpatient education on basic diabetes management are available (6,7).

Glycemic Targets

Improved metabolic control reduces both the onset and progression of diabetes-related complications in adults and adolescents with type 1 diabetes (8,9). Knowledge of glycemic targets by

Conflict of interest statements can be found on page S242.

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Table 1
Recommended glycemic targets for children and adolescents with type 1 diabetes

Age (years)	A1C (%)	Fasting/ preprandial PG (mmol/L)	2-hour postprandial PG* (mmol/L)	Considerations
<18	≤7.5	4.0–8.0	5.0–10.0	Caution is required to minimize severe or excessive hypoglycemia. Consider preprandial targets of 6.0–10.0 mmol/L as well as higher A1C targets in children and adolescents who have had severe or excessive hypoglycemia or have hypoglycemia unawareness.

A1C, glycated hemoglobin; *PG*, plasma glucose.
* Postprandial monitoring is rarely done in young children except for those on continuous subcutaneous insulin infusion (CSII) therapy for whom targets are not available.

the child with diabetes and parents and consistent target setting by the diabetes health-care team have been shown to be associated with improved metabolic control (10). Aggressive attempts should be made to reach the recommended glycemic target outlined in Table 1; however, clinical judgement is required to determine which children can reasonably and safely achieve these targets without severe or recurrent hypoglycemia. Results from a large multicentre observational study found that glycated hemoglobin (A1C) targets of ≤7.5% can be safely achieved without an increase in the risk of severe hypoglycemia in children less than 6 years of age (11). In some follow-up studies, episodes of severe hypoglycemia have been associated with poorer cognitive function, such as with memory and learning, whereas other studies have found that chronic hyperglycemia and glycemic variability in young children (ages 4 to 10 years) are associated with white matter structural changes and poorer overall cognitive performance (12–15). Young age at diabetes onset (under 7 years of age) has also been associated with poorer cognitive function (16). Treatment goals and strategies must be tailored to each child, with consideration given to individual risk factors.

Insulin Therapy

Insulin therapy is the mainstay of medical management of type 1 diabetes. A variety of insulin regimens can be used, but few have been studied specifically in children with new-onset diabetes. The choice of insulin regimen depends on many factors, including the child's age, duration of diabetes, family lifestyle, school support, socioeconomic factors, and family, patient, and physician preferences. Regardless of the insulin regimen used, all children should be treated to meet glycemic targets.

The honeymoon period, which can last up to 2 years after diagnosis, is characterized by target glycemic control and low insulin requirements (<0.5 units/kg/day). At the end of this period, more intensive management may be required to continue meeting glycemic targets. Two methods of intensive diabetes management have been used: basal-bolus regimens (long-acting basal insulin analogues and rapid-acting bolus insulin analogues) and continuous subcutaneous insulin infusion (CSII) therapy. Basal-bolus therapy has resulted in improved control over traditional twice-daily neutral protamine Hagedorn (NPH) and rapid-acting bolus analogue therapy in some but not all studies (17–19).

CSII is safe and effective and can be initiated at any age (20–22). A Cochrane review found that CSII resulted in slightly improved metabolic control over basal-bolus therapy (23). Some clinic-based studies of CSII in school-aged children and adolescents have shown a significant reduction in A1C with reduced hypoglycemia 12 to 24 months after initiation of CSII when compared to pre-CSII levels (24) or in the longer term when compared to controls on injections (25). Young age, A1C at CSII initiation and number of daily boluses may be associated with improved or sustained near-normal metabolic outcome (26). The Sensor-Augmented Pump Therapy for A1C Reduction (STAR) 3 study demonstrated that sensor-augmented insulin-pump therapy was more effective in lowering A1C levels than multiple daily injections (MDI) in children with poorly controlled type 1 diabetes mellitus (27).

Most, but not all, pediatric studies of the long-acting basal insulin analogues (detemir, glargine and degludec) have demonstrated improved fasting blood glucose (FBG) levels and fewer episodes of nocturnal hypoglycemia with a reduction in A1C (17,28–32). Two large population-based observational studies have not found improved A1C in children with diabetes using basal-bolus therapy or CSII when compared to those using NPH and rapid-acting bolus analogues (33,34). Insulin therapy should be individualized to reach A1C targets, minimize hypoglycemia and optimize quality of life.

Glucose Monitoring

Self-monitoring of blood glucose (SMBG) is an essential part of management of type 1 diabetes, and increased frequency has been associated with better clinical outcomes (35–37). Evidence of a strong association between frequency of SMBG and hemoglobin A1C levels has been found in T1D Exchange Clinic Registry participants (37). Subcutaneous continuous glucose sensors allow detection of asymptomatic hypoglycemia and hyperglycemia. In some studies, use of continuous glucose monitoring (CGM) has resulted in improved glycemic control with less hypoglycemia (38–40). In 1 larger randomized controlled trial of 322 adults and children, use of CGM was associated with improved glycemic control in adults but not in children and adolescents (41). Glycemic benefit correlated with duration of sensor use, which was much lower in children and adolescents (42). Recently, a built-in algorithm in an available CSII device with low glucose suspend feature has been shown to significantly lower overnight hypoglycemia (43,44).

Closed-Loop Pancreas System

The closed-loop pancreas system, also known as the artificial or bionic pancreas system, is one of the most rapidly evolving areas of clinical care for type 1 diabetes. It couples the use of an insulin pump with infusion of 1 or more hormones (insulin +/- glucagon), a glucose sensor and an algorithm for glucose control. The closed-loop system allows for decreasing excursions in blood glucose levels while reducing the overall burden of self-care. However, the system must ensure patient safety as well as prevent the occurrence of severe hypo- and hyperglycemia, as well as DKA. Results from several studies are promising for outcomes combining a lowering of the number of hypoglycemic events while optimizing per cent time in target range for glucose, fasting blood glucose and mean sensor glucose (45). However, most studies are short term and assessed the closed-loop system in different clinical settings. Larger randomized clinical trials in adults and youth are currently underway.

Nutrition

All children with type 1 diabetes should receive counselling from a registered dietitian experienced in pediatric diabetes. Children with

Table 2
Examples of carbohydrates for treatment of mild-to-moderate hypoglycemia

Patient age	<5 yrs	5 to 10 yrs	>10 yrs
Amount of carbohydrate	5 g	10 g	15 g
Carbohydrate Source			
Glucose tablet (4 g)	1	2 or 3	4
Dextrose tablet (3 g)	2	3	5
Apple or orange juice; regular soft drink; sweet beverage (cocktails)	40 mL	85 mL	125 mL

diabetes should follow a healthy diet as recommended for children without diabetes in *Eating Well with Canada*'s *Food Guide* (46). This involves consuming a variety of foods from the 4 food groups (grain products, vegetables and fruits, milk and alternatives, and meat and alternatives). Children with diabetes have been found to consume a diet that is similar to children without diabetes, one that is higher in fat and lower in fibre than guidelines recommend for healthy eating (47). Carbohydrate counting is a commonly used method of matching insulin to carbohydrate intake that allows increased flexibility in diet, although fat and protein content also influence postprandial glucose levels. There is no strong evidence that one form of nutrition therapy is superior to another in attaining age-appropriate glycemic targets. Nutrition therapy should be individualized (based on the child's nutritional needs, eating habits, lifestyle, ability and interest) and must ensure normal growth and development without compromising glycemic control. This plan should be evaluated regularly and at least annually. Features suggestive of eating disorders and of celiac disease should be systematically sought out (48).

Treatment of Hypoglycemia

Hypoglycemia is a major obstacle for children with type 1 diabetes and can affect their ability to achieve glycemic targets. Children with early-onset diabetes are at greatest risk for disruption of cognitive function and neuropsychological skills, but the respective roles of hypoglycemia and hyperglycemia in their development are still questioned (16,49). Significant risk of hypoglycemia often necessitates less stringent glycemic goals, particularly for younger children. There is no evidence in children that one insulin regimen or mode of administration is superior to another for resolving nonsevere hypoglycemia. As such, treatment must be individualized (50). Frequent use of CGM in a clinical care setting may reduce episodes of hypoglycemia (51).

Severe hypoglycemia should be treated with pediatric doses of intravenous dextrose in the hospital setting or glucagon in the home setting. In children, the use of mini-doses of glucagon has been shown to be useful in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate. A dose of 10 micrograms (mcg) per year of age (the equivalent of 1 unit on the syringe per year of age) (minimum dose 20 mcg (2 units), maximum dose 150 mcg (15 units)) is effective at treating and preventing hypoglycemia, with an additional doubled dose given if the BG has not increased in 20 minutes (52,53). Treatment of mild hypoglycemia is described in Table 2.

Chronic Poor Metabolic Control

A careful multidisciplinary assessment should be undertaken for every child with chronically poor metabolic control (e.g. A1C >10%) to identify potential causative and associated factors, such as depression (54), eating disorders (55), lower socioeconomic status, lower family support and higher family conflict (56,57), and to identify and address barriers to improved glycemic control. Use of a standardized measure of risk factors has been shown to identify those at high risk for poor control, emergency room visits and DKA (58). Glycemic control may be particularly challenging during adolescence due to physiologic insulin resistance, depression and other psychological issues, and reduced adherence during a time of growing independence. Multipronged interventions that target emotional, family and coping issues have shown a modest reduction in A1C with reduced rates of hospital admission (59–61).

Physical Activity

Inadequate levels of physical activity are common in all children, including those with diabetes. Increased physical activity is associated with better metabolic control. Two recent systematic reviews with meta-analyses have shown A1C reductions of ~0.5% with interventions aimed at increasing physical activity (62,63).

DKA

DKA occurs in approximately 40% of children with new-onset diabetes (range of 28% to 40% across United States centres and 11% to 67% across European centres), and at a frequency of one to 10 episodes per 100 patient-years in those with established diabetes (64,65). DKA continues to be the leading cause of morbidity and mortality in children with diabetes; subtle, persistent changes in brain structure and function ensuing from DKA are being increasingly appreciated (66–68). Children younger than 3 years of age and from areas with low prevalence of diabetes are especially at risk for moderate-to-severe DKA at the time of diagnosis (65). DKA can be prevented through earlier recognition and initiation of insulin therapy. Public awareness campaigns about the early signs of diabetes have significantly reduced the frequency of DKA in new-onset diabetes (69,70). In children with established diabetes, DKA results from failing to take insulin or poor sick-day management. Sick-day management includes more frequent SMBG, ketone measurement during hyperglycemia and adjustment of insulin dose in response to monitoring (71). Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children on CSII or long-acting basal insulin analogues, ethnic minorities, and children with psychiatric disorders and those with difficult family circumstances (72–75). The frequency of DKA in established diabetes can be decreased with education, behavioural intervention and family support (76,77), as well as access to 24-hour telephone services or telemedicine for parents of children with diabetes (78–80).

Management of DKA

While most cases of DKA are corrected without event, 0.5% to 1% of pediatric cases are complicated by cerebral edema (81), which is associated with significant morbidity (21% to 35%) and mortality (21% to 24%) (82). In contrast, cerebral edema has rarely been reported in adults (82). Although the cause of cerebral edema is still unknown, several factors are associated with increased risk (Table 3) (83–87). A bolus of insulin prior to infusion is not recommended since it does not offer faster resolution of acidosis (88,89) and may contribute to cerebral edema (90). Early insulin administration (within the first hour of fluid replacement) may increase the risk for cerebral edema (87). Special caution should be exercised in young children with DKA and new-onset diabetes or a greater degree of acidosis and extracellular fluid volume depletion because of the increased risk of cerebral edema.

Table 3
Risk factors for cerebral edema during treatment of diabetic ketoacidosis in children

- Younger age (<5 years)
- New-onset diabetes
- Greater severity of acidosis (lower pH and bicarbonate)
- High initial serum urea
- Low initial partial pressure of arterial carbon dioxide (pCO2)
- Rapid administration of hypotonic fluids
- IV bolus of insulin
- Early IV insulin infusion (within first hour of administration of fluids)
- Failure of serum sodium to rise during treatment
- Use of bicarbonate

IV, intravenous.

In some centres, it is common practice to initiate an intravenous insulin infusion at a rate of 0.05 units/kg/hour. One recent, prospective randomized controlled study suggests that an initial insulin infusion rate of 0.05 units/kg/hour is safe and effective, but this lower starting rate was not studied among those presenting in more severe or complicated DKA (91). Either mannitol or hypertonic saline can be used in the treatment of cerebral edema, but there is still insufficient evidence to favor one over the other; hypertonic saline use has been associated with increased mortality in a single, retrospective study (92). DKA should be managed according to published protocols for management of pediatric DKA (Figure 1) (93).

Vaccination

Historically, national guidelines have recommended influenza vaccination for children with type 1 diabetes (94,95). Currently, there is no evidence supporting increased morbidity or mortality from influenza in children with type 1 diabetes (96,97). However, the management of type 1 diabetes can be complicated by illness, requiring parental knowledge of sick-day management and increased attention during periods of illness. For this reason, parents may choose to have their children vaccinated.

Smoking Prevention and Cessation

Smoking is a significant risk factor for both cardiovascular (CV) and microvascular complications of diabetes (98) and, in adolescents, is associated with worse metabolic control (99). Smoking prevention should be emphasized throughout childhood and adolescence. The Canadian Paediatric Society website contains useful resources to promote smoking cessation among adolescents (http://www.cps.ca/en/documents/position/smoking-cessation) (100).

Alcohol and Substance Use

Adolescents with diabetes have similar rates of alcohol use and similar or higher rates of illicit drug use compared to adolescents without diabetes (101). Regular counselling should be provided around alcohol and substance use.

Contraception and Sexual Health Counselling

Adolescents with diabetes should receive regular counselling about sexual health and contraception. Unplanned pregnancies should be avoided, as pregnancy in adolescent females with type 1 diabetes with suboptimal metabolic control may result in higher risks of maternal and fetal complications than in older women with type 1 diabetes who are already at increased risk compared to the general population (102). Oral contraceptives, intrauterine devices and barrier methods can be used safely in the vast majority of adolescents (103).

Psychological Issues

For children, and particularly adolescents, there is a need to identify psychological disorders associated with diabetes and to intervene early to minimize the impact over the course of development. Children and adolescents with diabetes have significant risks for psychological problems, including diabetes distress (104), depression (105), anxiety (105), eating disorders and externalizing disorders (106–110). The risks increase during adolescence and emerging adulthood (111–113). Studies have shown that psychological disorders predict poor diabetes management and control (54,105,114–117) and, consequently, negative medical outcomes (118–121). Conversely, as glycemic control worsens, the probability of psychological problems increases (122).

The presence of psychological symptoms and diabetes problems in children and adolescents is often strongly affected by caregiver/family distress. Research has demonstrated that while parental psychological issues may distort perceptions of the child's diabetes control (123), they are often related to poor psychological adjustment and diabetes control (124–127). Maternal anxiety and depression are associated with poor diabetes control in younger adolescents and with reduced positive affect and motivation in older teens (128).

Eating disorders

Ten per cent of adolescent females with type 1 diabetes meet the *Diagnostic and Statistical Manual of Mental Disorders* (4th Edition) criteria for eating disorders compared to 4% of their age-matched peers without diabetes (129). Disordered eating with insulin restriction is also seen in youth with diabetes (130). Furthermore, eating disorders are associated with poor metabolic control (55) and earlier onset and more rapid progression of microvascular complications (131). Eating disorders should be suspected in those adolescent and young adult females who are unable to achieve and maintain metabolic targets, especially when insulin omission is suspected. It is important to identify individuals with eating disorders because different management strategies are required to optimize metabolic control and prevent microvascular complications (129,131,132).

Prevention and intervention

Children and adolescents with diabetes, along with their families, should be screened throughout their development for psychological disorders (133). Given the prevalence of psychological issues, screening in this area can be seen as equally important as screening for microvascular complications in children and adolescents with diabetes (134).

Psychological interventions with children and adolescents, as well as families, have been shown to improve mental health (106,135), including overall well-being and perceived quality of life (136), along with depressive symptoms (137,138). In addition, there is some evidence that psychosocial interventions can positively affect glycemic control (59,135,139). Most importantly, some studies have demonstrated that psychological interventions can increase diabetes treatment adherence, improve glycemic control and improve psychosocial functioning (140,141).

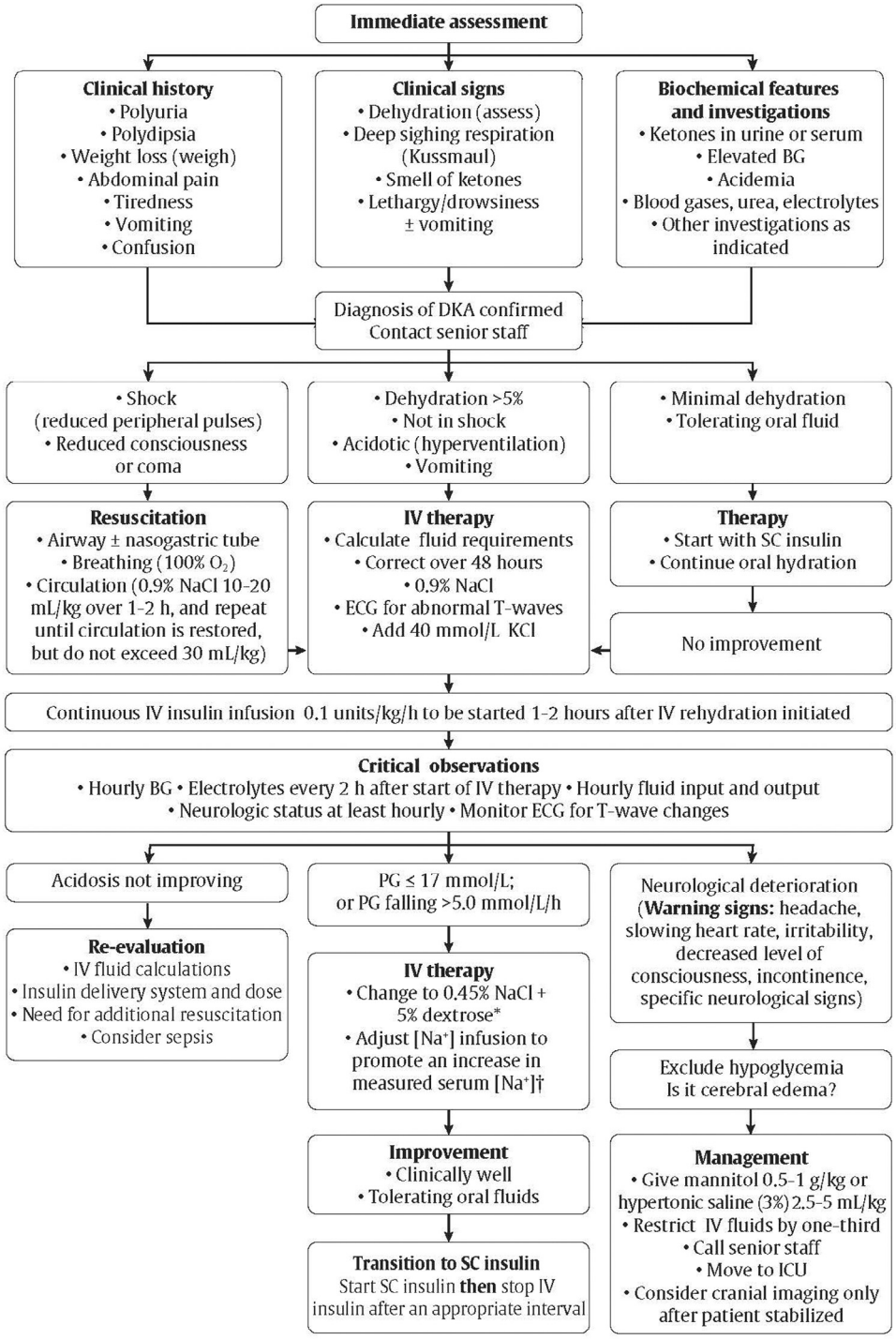

Figure 1. Immediate assessment and management of diabetic ketoacidosis in children.
BG, blood glucose; *D5W*; 5% dextrose in water; *D10W*; 10% dextrose in water; *D12.5W*: 12.5% dextrose in water; *DKA*; diabetic ketoacidosis; *ECG*, electrocardiogram; *ICU*, intensive care unit; *IV*, intravenous; *NaCl*; sodium chloride; *PG*, plasma glucose; *SC*, subcutaneous. Adapted with permission from reference 93.

Comorbid Conditions

Autoimmune thyroid disease

Clinical autoimmune thyroid disease (AITD) occurs in 15% to 30% of individuals with type 1 diabetes (142). The risk for AITD during the first decade of diabetes is directly related to the presence or absence of anti-thyroid antibodies (i.e. thyroid peroxidase antibodies) at diabetes diagnosis (143). Hypothyroidism is most likely to develop in girls at puberty (144). Early detection and treatment of hypothyroidism will prevent growth failure and symptoms of hypothyroidism (Table 4). Hyperthyroidism also occurs more

Table 4
Recommendations for screening for comorbid conditions in children with type 1 diabetes

Condition	Indications for screening	Screening test	Frequency
Autoimmune thyroid disease	All children with type 1 diabetes	Serum TSH level + thyroid peroxidase antibodies	At diagnosis and every 2 years thereafter; thyroperoxidase antibodies do not need to be repeated if previously positive
	Positive thyroid antibodies, symptoms of thyroid disease or goiter	Serum TSH level (+thyroid peroxidase antibodies if previously negative)	Every 6–12 months
Primary adrenal insufficiency	Unexplained recurrent hypoglycemia and decreasing insulin requirements	8 AM serum cortisol and serum sodium and potassium	As clinically indicated
Celiac disease	Recurrent gastrointestinal symptoms, poor linear growth, poor weight gain, fatigue, anemia, unexplained frequent hypoglycemia or poor metabolic control	Tissue transglutaminase + immunoglobulin A levels	As clinically indicated

TSH, thyroid-stimulating hormone.

Table 5
Screening for diabetes complications, dyslipidemia and hypertension in children with type 1 diabetes

Complication/ Comorbidity	Indications and intervals for screening	Screening method
Nephropathy	• Yearly screening commencing at 12 years of age in those with duration of type 1 diabetes >5 years	• First morning (preferred) or random urine ACR • Abnormal ACR requires confirmation at least 1 month later with a first morning ACR and, if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate • Repeated sampling should be done every 3–4 months over a 6- to 12-month period to demonstrate persistence
Retinopathy	• Yearly screening commencing at 15 years of age with duration of type 1 diabetes >5 years • Screening interval can increase to 2 years if good glycemic control, duration of diabetes <10 years and no retinopathy at initial assessment	• 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or • Digital fundus photography
Neuropathy	• Children ≥15 years with poor metabolic control should be screened yearly after 5 years of type 1 diabetes	• Question and examine for symptoms of numbness, pain, cramps and paresthesia, as well as skin sensation, vibration sense, light touch and ankle reflexes
Dyslipidemia	• Delay screening post-diabetes diagnosis until metabolic control has stabilized • Screen at 12 and 17 years of age • <12 years of age: screen only those with BMI >97th percentile, family history of hyperlipidemia or premature CVD	• Fasting or non-fasting TC, HDL-C, TG, calculated LDL-C. Measurement of non-fasting lipids may be considered if TG are not elevated.
Hypertension	• Screen all children with type 1 diabetes at least twice a year	• Use appropriate cuff size

ACR, albumin to creatinine ratio; *BMI*, body mass index; *CVD*, cardiovascular disease; *HDL-C*; high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TC*, total cholesterol; *TG*, triglycerides.

frequently in association with type 1 diabetes than in the general population.

Primary adrenal insufficiency (Addison's disease)

Primary adrenal insufficiency is rare, even in those with type 1 diabetes (145). Targeted screening is required in those with unexplained recurrent hypoglycemia and decreasing insulin requirements (Table 4).

Celiac disease

Celiac disease can be identified in 4% to 9% of children with type 1 diabetes (142), but in 60% to 70% of these children, the disease is asymptomatic (silent celiac disease). Children with type 1 diabetes are at increased risk for classic or atypical celiac disease during the first 10 years of diabetes (146). There is good evidence that treatment of classic or atypical celiac disease with a gluten-free diet improves intestinal and extraintestinal symptoms (147), and prevents the long-term sequelae of untreated classic celiac disease (148). However, there is no evidence that untreated asymptomatic celiac disease is associated with short- or long-term health risks (149,150) or that a gluten-free diet improves health in these individuals (151). Thus, universal screening for and treatment of asymptomatic celiac disease remains controversial (Table 4).

Diabetes Complications

There are important age-related considerations regarding surveillance for diabetes complications and interpretation of investigations (Table 5). Risk for microvascular complications accelerates through puberty (152,153). In an observational study, children with type 1 diabetes with a mean duration of 7.9 years were found to have an age-adjusted prevalence of diabetic nephropathy of 5.8%, retinopathy 5.6%, peripheral neuropathy 8.5%, arterial stiffness 11.6%, hypertension 10.1% and cardiovascular (CV) autonomic neuropathy 14.4% (154).

Chronic kidney disease

Prepubertal children and those in the first 5 years of diabetes should be considered at very low risk for albuminuria (152,155). A first morning urine albumin to creatinine ratio (ACR) has high sensitivity and specificity for the detection of albuminuria (156,157). Although screening with a random ACR is associated with greater compliance than with a first morning sample, its specificity may be compromised in adolescents due to their higher frequency of exercise-induced proteinuria and benign postural proteinuria. Abnormal random ACRs (i.e. >2.5 mg/mmol) require confirmation with a first morning ACR or timed overnight urine collection (158).

The likelihood of transient or intermittent albuminuria is higher during the early peripubertal years (155). Individuals with intermittent albuminuria may progress to overt nephropathy (159). Abnormal screening results require confirmation and follow up to demonstrate persistent abnormalities, as albuminuria can and is more likely to regress in youth compared to older adults (160–162).

Treatment is indicated only for those adolescents with persistent albuminuria. One short-term randomized controlled trial in adolescents demonstrated that angiotensin-converting enzyme (ACE) inhibitors were effective in reducing albuminuria compared to placebo (163). However, there are no long-term intervention studies assessing the effectiveness of ACE inhibitors or angiotensin receptor blockers (ARBs) in delaying progression to overt nephropathy in adolescents with albuminuria. Therefore, treatment of adolescents with persistent albuminuria is based on the effectiveness of treatments in adults with type 1 diabetes (164).

Retinopathy

Retinopathy is rare in prepubertal children with type 1 diabetes and in postpubertal adolescents with good metabolic control (153,165–167). Earlier reductions in A1C during adolescence and attention to blood pressure (BP) control may stave off sight-threatening diabetic retinopathy in adulthood (153).

Neuropathy

When present, neuropathy is mostly subclinical in children (168). While prospective nerve conduction studies and autonomic neuropathy assessment studies have demonstrated increased prevalence of abnormalities over time (169), persistence of abnormalities is an inconsistent finding (170). There are very few studies assessing the diagnostic utility of noninvasive screening methods in children with diabetes; among them, vibration and monofilament testing have suboptimal sensitivity and specificity in adolescents. Normative thresholds vary with age and gender (171). With the exception of intensifying diabetes management to achieve and maintain glycemic targets, no other treatment modality has been studied in children and adolescents.

Dyslipidemia

Most children with type 1 diabetes should be considered at low risk for cardiovascular disease (CVD) associated with dyslipidemia (172–174). The exceptions are those with longer duration of disease, microvascular complications or other CV risk factors, including smoking, hypertension, obesity (175) and/or family history of premature CVD (176). Dyslipidemia screening should be targeted at those greater than 12 years of age and younger children with specific risk factors for dyslipidemia. Measurement of non-fasting lipids is now recommenced for adults as long as triglycerides are not elevated. Evidence in children with diabetes is limited. Statin therapy has been studied specifically in children with diabetes, and while there is no evidence linking specific low-density lipoprotein cholesterol (LDL-C) cut-offs in children with diabetes with long-term outcomes, statin therapy has been shown to significantly lower LDL-C as well as lipoproteins (177). In pubertal children without diabetes but with familial hypercholesterolemia, statin therapy is known to be safe and effective at lowering LDL-C levels and attenuating progression of surrogate markers for future CVD (178). Different markers of future CVD are being explored to better predict when to intervene (179–182).

Hypertension

Up to 16% of adolescents with type 1 diabetes have hypertension (183). Twenty-four hour ambulatory BP monitoring has been used to exclude white coat hypertension and to identify loss of diurnal systolic rhythm (nondippers) with nocturnal hypertension in some normotensive adolescents with type 1 diabetes (184). These abnormalities may be predictive of future albuminuria (184). However, the role of ambulatory BP monitoring in routine care remains uncertain. Children with type 1 diabetes and confirmed hypertension should be treated according to the guidelines for children without diabetes (185).

Transition to Adult Care

Emerging adulthood, the developmental stage between ages 18 to 25 years, is a stage of life wherein the emerging adult is establishing his or her autonomy, personal identity, and making vocational and educational choices (186). For the emerging adult with diabetes, this stage is complicated by the transition from pediatric to adult care, a high-risk period characterized by inadequate medical follow up and self-management, deteriorating glycemic control, and an increased risk of adverse outcomes (187–190). Between 25% and 65% of young adults have no medical follow up during the transition from pediatric to adult diabetes care services (191–193). Those with no follow up are more likely to experience hospitalization for DKA during this period. Organized transition services may decrease the rate of loss of follow up and the risk of adverse outcomes (189,192,195–198). Further, initiating a transition plan in early adolescence (e.g. 12 years of age), that includes education in self-care behaviours, transition readiness assessments and identifying transition goals may be of benefit in preparing adolescents and their families for transition (199,200).

RECOMMENDATIONS

Delivery of Care

1. All children with diabetes should have access to an experienced pediatric DHC team that includes either a pediatric endocrinologist or pediatrician with diabetes expertise, dietician, diabetes nurse educator, social worker and mental health professional for specialized care starting at diagnosis [Grade D, Level 4 (1)].

2. Children with new-onset type 1 diabetes who are medically stable should receive their initial education and management in an outpatient setting, provided that appropriate personnel and daily communication with a DHC team are available [Grade B, Level 1A (6,7)].

3. To ensure ongoing and adequate diabetes care, adolescents should receive care from a specialized program aimed at creating a well-prepared and supported transition to adult care that is initiated early and includes a transition coordinator; patient reminders; and support and education promoting autonomy and self-care management skills [Grade C, Level 3 (189,191,192,194–197)].

Glycemic Targets

4. Children and adolescents <18 years of age should aim for an A1C target ≤7.5% [Grade D, Consensus]
   a. Attempts should be made to safely reach the recommended glycemic target, while minimizing the risk for severe or recurrent hypoglycemia. Treatment targets should be tailored to each child, taking into consideration individual risk factors for hypoglycemia [Grade D, Consensus]
   b. In children <6 years of age, particular care to minimize hypoglycemia is recommended because of the potential association in this age group between severe hypoglycemia and later cognitive impairment [Grade D, Level 4 (15)].

5. Children with persistently poor glycemic control (e.g. A1C >10%) should be assessed with a validated tool by a specialized pediatric DHC team for comprehensive interdisciplinary assessment and referred for

psychosocial support as indicated [Grade D, Consensus]. Intensive family and individualized psychological interventions aimed at improving glycemic control should be considered to improve chronically poor metabolic control [Grade A, Level 1A (59–61)].

Insulin Therapy

6. Children with new-onset diabetes should be started on boluses of rapid-acting insulin analogues combined with basal insulin (e.g. intermediate-acting insulin or long-acting basal insulin analogue) using an individualized regimen that best addresses the practical issues of daily life [Grade D, Consensus].

7. Insulin therapy should be assessed at each clinical encounter to ensure it still enables the child to meet A1C targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities [Grade D, Consensus]. If these goals are not being met, an intensified diabetes management approach (including increased education, monitoring and contact with diabetes team) should be used [Grade A, Level 1 (8) for adolescents; Grade D, Consensus for younger children], and treatment options may include the following:
   a. Increased frequency of injections [Grade D, Consensus]
   b. Change in the type of basal and/or bolus insulin [Grade B, Level 2 (29) for adolescents; Grade D, Consensus for younger children]
   c. Change to CSII therapy [Grade C, Level 3 (22)].

Treatment of Hypoglycemia

8. In children, the use of mini doses of glucagon (10 mcg per year of age with minimum dose 20 mcg and maximum dose 150 mcg) should be considered in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate [Grade D, Level 4 (52)].

9. In the home situation, severe hypoglycemia in an unconscious child >5 years of age should be treated with 1 mg glucagon subcutaneously or intramuscularly. In children ≤5 years of age, a dose of 0.5 mg glucagon should be given. The episode should be discussed with the DHC team as soon as possible and consideration given to reducing insulin doses for the next 24 hours to prevent further severe hypoglycemia [Grade D, Consensus].

10. Dextrose 0.5 to 1 g/kg should be given intravenously over 1–3 minutes to treat severe hypoglycemia with unconsciousness when intravenous access is available [Grade D, Consensus].

Physical Activity

11. Regular physical activity ≥3 times per week for ≥60 minutes each time should be encouraged for all children with diabetes [Grade A, Level 1 (62,63)].

Diabetic Ketoacidosis

12. To prevent DKA in children with diabetes:
   a. Targeted public awareness campaigns should be considered to educate parents, other caregivers (e.g. teachers) and health-care providers about the early symptoms of diabetes [Grade C, Level 3 (70,76)]
   b. Immediate assessment of ketone and acid-base status should be done in any child presenting with new-onset diabetes [Grade D, Consensus]
   c. Comprehensive education and support services [Grade C, Level 3 (77)], as well as 24-hour telephone services [Grade C, Level 3 (78)], should be available for families of children with diabetes.

13. DKA in children should be treated according to pediatric-specific protocols [Grade D, Consensus]. If appropriate expertise/facilities are not available locally, there should be immediate consultation with a centre with expertise in pediatric diabetes [Grade D, Consensus].

14. In children in DKA, rapid administration of hypotonic fluids should be avoided [Grade D, Level 4 (84)]. Circulatory compromise should be treated with only enough isotonic fluids to correct circulatory inadequacy [Grade D, Consensus]. Replacement of fluid deficit should be extended over a 48-hour period with regular reassessments of fluid status [Grade D, Level 4 (84)].

15. In children in DKA, an intravenous insulin bolus should not be given [Grade D, Consensus]. The insulin infusion should not be started for at least 1hour after starting fluid replacement therapy [Grade D, Level 4 (87)]. An intravenous infusion of short-acting insulin should be used at an initial dose of 0.05 to 0.1 units/kg/h, depending on the clinical situation [Grade A, Level 1A (91)].

16. In children in DKA, once blood glucose reaches ≤17.0 mmol/L, intravenous dextrose should be started to prevent hypoglycemia. The dextrose infusion should be increased, rather than reducing insulin, to prevent rapid decreases in glucose. The insulin infusion should be maintained until pH normalizes and ketones have mostly cleared [Grade D, Consensus].

17. In children in DKA, administration of sodium bicarbonate should be avoided except in extreme circulatory compromise, as this has been associated with cerebral edema [Grade D, Level 4 (83)].

18. In children in DKA, either mannitol or hypertonic saline may be used in the treatment of cerebral edema [Grade D, Level 4 (92)].

Microvascular Complications

19. Children ≥12 years with diabetes duration >5 years should be screened annually for CKD with a first morning urine ACR (preferred) [Grade B, Level 2 (157)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (161,162)] at least 1 month later with a first morning ACR and, if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate [Grade D, Consensus]. Albuminuria (ACR >2.5 mg/mmol; AER >20 mcg/min) should not be diagnosed unless it is persistent, as demonstrated by 2 consecutive first morning ACR or timed collections obtained at 3- to 4-month intervals over a 6- to 12-month period [Grade D, Consensus].

20. Children ≥12 years with persistent albuminuria should be treated per adult guidelines (see Chronic Kidney Disease in Diabetes chapter, p. S201) [Grade D, Consensus].

21. Children ≥15 years with 5 years' diabetes duration should be annually screened and evaluated for retinopathy by an expert professional [Grade C, Level 3 (167)]. The screening interval can be increased to every 2 years in children with type 1 diabetes who have good glycemic control, duration of diabetes <10 years and no significant retinopathy (as determined by an expert professional) [Grade D, Consensus].

22. Children ≥15 years with 5 years' diabetes duration and poor metabolic control should be questioned about symptoms of numbness, pain, cramps and paresthesia, and examined for skin sensation, vibration sense, light touch and ankle reflexes [Grade D, Consensus].

Comorbid Conditions and Other Complications

23. Children and adolescents with diabetes, along with their families, should be screened regularly for psychosocial or psychological disorders [Grade D, Consensus] and should be referred to an expert in mental health and/or psychosocial issues for intervention when required [Grade D, Consensus].

24. Adolescents with type 1 diabetes should be regularly screened using nonjudgmental questions about weight and body image concerns, dieting, binge eating and insulin omission for weight loss [Grade D, Consensus].

25. Children with type 1 diabetes who are <12 years of age should be screened for dyslipidemia if they have other risk factors, such as obesity (body mass index >97th percentile for age and gender) and/or a family history of dyslipidemia or premature CVD. Routine screening for dyslipidemia should begin at 12 years of age, with repeat screening after 5 years [Grade D, Consensus].

26. Once dyslipidemia is diagnosed in children with type 1 diabetes, the dyslipidemia should be monitored regularly and efforts should be made to improve metabolic control and promote healthy behaviours. While it can be treated effectively with statins, a specific LDL cut-off to initiate treatment is yet to be determined in this age category [Grade D, Consensus].

27. All children with type 1 diabetes should be screened for hypertension at least twice annually [Grade D, Consensus].

28. Children with type 1 diabetes and BP readings persistently above the 95th percentile for age should receive healthy behaviour counselling, including weight loss if overweight [Grade D, Level 4 (201)]. If BP remains elevated, treatment should be initiated based on recommendations for children without diabetes [Grade D, Consensus].

29. Influenza vaccination should be offered to children with diabetes as a way to prevent an intercurrent illness that could complicate diabetes management [Grade D, Consensus].

30. Formal smoking prevention and cessation counselling should be part of diabetes management for children with diabetes [Grade D, Consensus].

31. Adolescents should be regularly counselled around alcohol and substance use [Grade D, Consensus].

32. Adolescent females with type 1 diabetes should receive counselling on contraception and sexual health in order to prevent unplanned pregnancy [Grade D, Level 4 (202)].

33. Children with type 1 diabetes who have anti-thyroid antibodies should be considered at high risk for autoimmune thyroid disease [Grade C, Level 3 (143)]. Children with type 1 diabetes should be screened at diabetes diagnosis with repeat screening every 2 years using a serum thyroid-stimulating hormone and thyroid peroxidase antibodies [Grade D, Consensus]. More frequent screening is indicated in the presence of positive anti-thyroid antibodies, thyroid symptoms or goiter [Grade D, Consensus].

34. Children with type 1 diabetes and symptoms of classic or atypical celiac disease (see Table 4) should undergo celiac screening [Grade D, Consensus] and, if confirmed, be treated with a gluten-free diet to improve symptoms [Grade D, Level 4 (147)] and prevent the long-term sequelae of untreated classic celiac disease [Grade D, Level 4 (148)]. Discussion of the pros and cons of screening and treatment of asymptomatic celiac disease should take place with children and adolescents with type 1 diabetes and their families [Grade D, Consensus].

Abbreviations
A1C, glycated hemoglobin; *ACR*, albumin to creatinine ratio; *ACE*, angiotensin-converting enzyme; *AER*, albumin excretion rate; *AITD*, autoimmune thyroid disease; *ARB*, angiotensin receptor blocker; *BP*, blood pressure; *CGM*, continuous glucose monitoring; *CKD*, chronic kidney disease; *CV*, cardiovascular; *CVD*, cardiovascular disease; *CSII*, continuous subcutaneous insulin infusion; *DHC*, diabetes health care; *DKA*, diabetic ketoacidosis; *LDL-C*, low-density lipoprotein cholesterol; *MDI*, multiple daily injections; mcg, micrograms; *SMBG*, self-monitoring of blood glucose.

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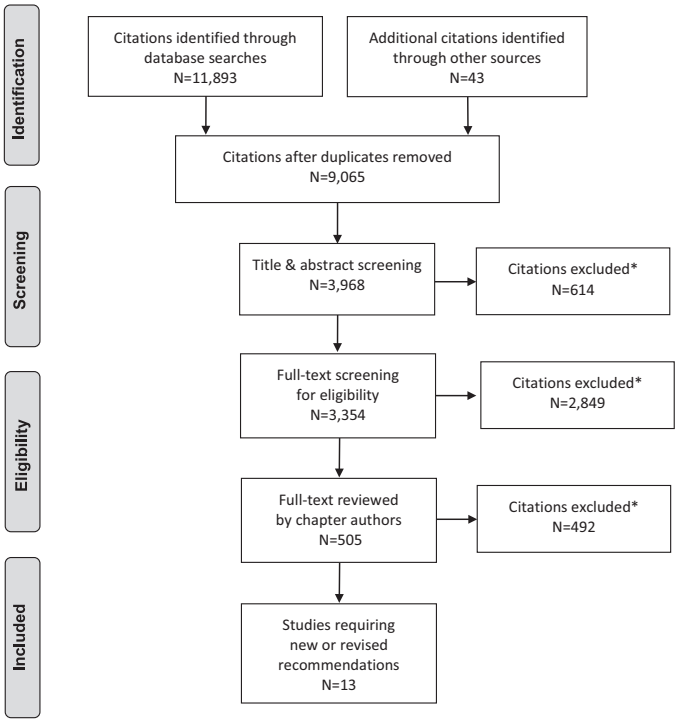
Literature Review Flow Diagram for Chapter 34: Type 1 Diabetes in Children and Adolescents



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (203).

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2018 Clinical Practice Guidelines

Type 2 Diabetes in Children and Adolescents

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Anticipatory guidance regarding healthy eating, physical activity, limiting screen time and age-appropriate sleep duration/quality is recommended to prevent type 2 diabetes in children and adolescents.
- Regular targeted screening for type 2 diabetes is recommended in children at risk.
- Children with type 2 diabetes should receive care in consultation with an interprofessional pediatric diabetes health-care team.
- Early screening, intervention and optimization of glycemic control are essential, as the onset of type 2 diabetes during childhood is associated with severe and early onset of microvascular and cardiovascular complications.

KEY MESSAGES FOR PEOPLE WITH CHILDREN AND ADOLESCENTS WITH DIABETES

- There is plenty you can do to help manage or prevent type 2 diabetes in children and adolescents. Encourage your child or adolescent to eat healthy foods, limit sweet drinks (juice, pop), get plenty of physical activity, get a good night's sleep and keep time spent on screens low.
- Many children with type 2 diabetes will also require oral glucose-lowering medication and/or insulin for treatment.

Note: Unless otherwise specified, the term "child" is used for individuals 0 to 18 years of age, and the term "adolescent" for those 13 to 18 years of age.

Introduction

Type 2 diabetes in children has increased in frequency around the world over the past 2 decades (1). Children from ethnic groups at high risk for type 2 diabetes in their adult populations, namely those of African, Arab, Asian, Hispanic, Indigenous or South Asian descent, are disproportionately affected. A Canadian national surveillance study demonstrated a minimum incidence of type 2 diabetes in children and adolescents <18 years of age of 1.54 per 100,000 children per year (2). Significant regional variation was observed with the highest minimum incidence seen in Manitoba of 12.45 per 100,000 children per year. In this study, 44% of children with new-onset type 2 diabetes were of Aboriginal heritage, 25% Caucasian, 10.1% Asian, 10.1% African/Caribbean and the remaining of other or mixed ethnic origin (2). Recent data from the United States demonstrated an incidence of 8.1 per 100,000 person years in the 10- to 14-year age group and 11.8 per 100,000 person years in the 15- to 19-year age group. In this study, the highest rates were found in American Indian, African American, Asian/Pacific Islander and Hispanic youth (in descending order), and the lowest incidence occurred in non-Hispanic white youth (3). Type 2 diabetes is a highly heritable condition, with 90% of children and youth affected having a first- or second-degree relative who also has type 2 diabetes (4). A significant proportion of youth with type 2 diabetes live below the poverty line or come from low-resourced homes (5).

Prevention

Breastfeeding has been shown to reduce the risk of youth-onset type 2 diabetes in some populations (6).

Obesity is a major risk factor for the development of type 2 diabetes (2). The prevalence of obesity among Canadian children aged 5 to 17 years is 12% (7). Studies on the prevention of obesity in children are limited and have generally not demonstrated long-term effectiveness (8,9).

Efforts to improve sleep quality and quantity, decrease sedentary behaviours and increase both light and vigorous physical activity can result in significant metabolic health benefits (10,11). Health Canada has endorsed the Canadian 24-hour Movement Guidelines for children and youth (available at http://www.csep.ca/en/guidelines/get-the-guidelines) (12).

Interventions aimed at reducing sugar-sweetened beverage consumption among children and youth should also be considered as consumption of these beverages has been linked to both obesity and incident type 2 diabetes (13–15). Screen time use should be limited, given its relationship to greater insulin resistance and adiposity (16).

In children with obesity, family-based healthy behaviour interventions, which include physical activity, healthy nutrition and mental health supports have been shown to result in a modest decrease in body mass index (BMI) and improvements in metabolic health parameters. The most effective interventions were those delivered by a specialized interdisciplinary team that included group sessions with parent and family involvement (9).

In adolescents with obesity, pharmacotherapy (i.e. orlistat or metformin) in combination with healthy behaviour interventions, demonstrate a very modest additional reduction in BMI over the short term, with frequent gastrointestinal side effects (17). Long-term studies are absent, and no pediatric studies have been

Conflict of interest statements can be found on page S252.

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performed to assess the prevention of diabetes or long-term complications using these medications (17). In adolescents with obesity and evidence of severe insulin resistance, pharmacological therapy with metformin or orlistat should only be considered after a comprehensive evaluation of the child's metabolic status, family history and review of healthy behaviour interventions. Due to a lack of data in prepubertal children, the use of weight management medications should only be considered in this population within the context of a supervised clinical trial (17–19).

Bariatric surgery may be considered in adolescents with severe obesity (BMI ≥35 kg/m^2 with severe comorbidities or ≥40 kg/m^2 with less severe comorbidities), who have reached their final adult height and have undergone a comprehensive assessment by an expert interprofessional team, affirming their understanding of the risks and benefits of the procedure, demonstrating their ability to adhere to the necessary pre- and post-operative care, and have appropriate family and social supports (20) (see Weight Management in Diabetes chapter, p. S124). The long-term effectiveness of bariatric surgery remains unknown.

Screening and Diagnosis

The microvascular complications of type 2 diabetes have been identified at diagnosis, implying long-term, unrecognized hyperglycemia (21). Children may also present with acute decompensation in diabetic ketoacidosis (DKA) and/or hyperosmolar hyperglycemic state (HHS). This argues for a systematic screening program in children at high risk for type 2 diabetes in order to prevent an acute, life-threatening presentation and to decrease the development of chronic complications. Although not proven in children, it is generally assumed that earlier diagnosis of diabetes will lead to interventions that will improve glycemic control and reduce the related short- and long-term complications (21).

Risk factors for the development of type 2 diabetes in children include a history of type 2 diabetes in a first- or second-degree relative (1–4,22), being a member of a high-risk population (e.g. people of African, Arab, Asian, Hispanic, Indigenous or South Asian descent) (1–4); obesity (2); impaired glucose tolerance (IGT) (23); polycystic ovary syndrome (PCOS) (24); exposure to diabetes in utero (25–27); acanthosis nigricans (28); hypertension and dyslipidemia (29); and non-alcoholic fatty liver disease (NAFLD) (30). Atypical antipsychotic medications are associated with significant weight gain, insulin resistance and impaired fasting glucose (IFG) or type 2 diabetes in children (31–33). Neuropsychiatric disorders and the use of neuropsychiatric medications are more common in children with obesity and type 2 diabetes compared to the general pediatric population (34).

In a recent national Canadian diabetes incidence study, the mean age of diagnosis of type 2 diabetes in youth was 13.7 years (2). However, 8% of all newly diagnosed children with type 2 diabetes were less than 10 years of age. In children of Aboriginal, Caucasian and Asian origin, 11%, 8.8% and 8.7%, respectively, presented at less than 10 years of age. Thus, consideration should be given for screening at a younger age in those at high risk (2).

A fasting plasma glucose (FPG) is the recommended routine screening test for children, although ensuring a fasting state may be a challenge. The reproducibility of the FPG is high (35). The oral glucose tolerance test (OGTT) may have a higher detection rate (36,37) in children who have severe obesity (BMI ≥99th percentile for age and gender) and who have multiple risk factors for type 2 diabetes, but it has poor reproducibility (35). A glycated hemoglobin (A1C) ≥6.0% is able to identify children with type 2 diabetes at 86% sensitivity and 85% specificity and had similar screening efficacy to FPG, when compared to the gold standard 2-hour OGTT (38), using laboratory-based, DCCT-aligned, National Glycohemoglobin Standardization program-certified methodology. In children with insulin resistance, the screening efficacy of A1C improved to 99% sensitivity and 96% specificity (38). A1C offers a more practical alternative to fasting blood work and/or a 2-hour OGTT, and is predictive of future diabetes-related complications (39). Limitations include heterogeneous assay methodologies, inaccuracy in the presence of hemoglobinopathies or hemolysis and an inability to accurately predict IGT or IFG. The use of A1C as a screening test for pediatric diabetes is controversial because it diverges to some extent from fasting blood glucose values and post-glucose challenge values. Therefore, A1C should not be relied upon as the sole diagnostic test to screen for type 2 diabetes but rather used in combination with FPG and/or 2-hour OGTT. Given the aforementioned limitations, we recommend using a combination of A1C and fasting or random blood glucose to screen for type 2 diabetes in children and youth with risk factors. A 2-hour OGTT may be considered as an initial screening test in children and youth with 3 or more risk factors and should be done in those in whom there is a discrepancy between the A1C and fasting or random blood glucose results.

Classification

In most children, the presence of clinical risk factors, mode of presentation and early course of the disease indicate whether the child has type 1 or type 2 diabetes. However, differentiation may be difficult in some. Children with type 2 diabetes can present with DKA (40,41). Testing for diabetes autoantibodies should be considered in all children and adolescents with a clinical diagnosis of type 2 diabetes because of evidence that up to 10% to 20% of these children are autoantibody positive, suggesting that they, in fact, have type 1 diabetes with insulin deficiency and are at risk for other autoimmune conditions (42). In addition, the absence of islet autoantibodies may be useful in supporting the diagnosis of type 2 diabetes (43–45). Fasting insulin levels are not helpful at diagnosis, as levels may be low due to glucose toxicity (46). DNA diagnostic testing for genetic defects in beta cell function (monogenic diabetes) should be considered in children who have a strong family history suggestive of autosomal dominant inheritance and who are lacking features of insulin resistance. This may be helpful when diabetes classification is unclear and may lead to more appropriate management (47,48).

Management

Children with type 2 diabetes should receive care in conjunction or consultation with an interprofessional pediatric diabetes health-care team that should include either a pediatric endocrinologist or pediatrician with diabetes expertise, dietitian, diabetes nurse educator and mental health professional. The target A1C for most children with type 2 diabetes should be ≤7.0%. However, there is evidence to suggest that achieving an A1C of <6.0% within the first 6 months of diagnosis may reduce the risk of treatment failure (49). To be effective, treatment programs for adolescents with type 2 diabetes need to address the lifestyle and health habits of the entire family, emphasizing healthy eating and physical activity (50), and promoting smoking prevention/cessation strategies.

In adolescent females with type 2 diabetes, proactive contraceptive counselling to avoid pregnancy is warranted given the high rates of congenital anomalies reported in this population (51).

A recent quality improvement initiative using anonymized data from 578 adolescents with type 2 diabetes in Germany and Austria found that more than half of these adolescents did not perform regular physical activity, and increasing physical activity was associated with a lower A1C, a lower body mass index-standard

deviation score (BMI-SDS) and a higher high-density lipoprotein cholesterol (HDL-C) (52). In addition, the SEARCH for Diabetes in Youth Study found that decreased time spent watching television was associated with a significantly attenuated 5-year increase in A1C among adolescents with type 2 diabetes (53). Thus, it is reasonable to recommend (in the absence of direct evidence for this population [54]) that children with type 2 diabetes strive to achieve the same activity level recommended for children in general (i.e. 60 minutes daily of moderate-to-vigorous physical activity; limiting recreational screen time to no more than 2 hours per day and limiting sedentary (motorized) transport, extended sitting and time spent indoors throughout the day (http://www.csep.ca/en/guidelines/get-the-guidelines) (12).

Insulin is required in those with severe metabolic decompensation at diagnosis (e.g. DKA, A1C ≥9.0%, symptoms of severe hyperglycemia) but may be successfully weaned once glycemic targets are achieved (55,56). Once-a-day basal insulin is often effective in attaining metabolic control. Unless acidosis is present, metformin should generally be started at the same time as insulin, at a starting dose of 500 mg daily for 7 days, titrating by 500 mg once a week over 3 to 4 weeks to a maximum dose of 1,000 mg twice daily. Titration increments may be reduced to 250 mg if there are gastrointestinal side effects.

While none of the noninsulin antihyperglycemic agents have been approved by Health Canada for use in children, there are increasing data about the safety or efficacy of certain noninsulin antihyperglycemic agents in the pediatric population. Metformin was the first to be shown in a randomized controlled trial to be safe in adolescents for up to 16 weeks, reducing A1C by 1.0% to 2.0% and lowering FPG with similar side effects as seen in adults (57). Glimepiride has since also been shown to be safe and effective in adolescents for up to 24 weeks, reducing A1C (-0.54%) to a similar extent as metformin (-0.71%), but resulting in a significant weight increase of 1.3 kg (58). For this reason, glimepiride should only be considered if metformin is not tolerated.

The Treatment Options for Type 2 Diabetes in Youth (TODAY) study was a multicentre trial that randomized 699 youth with type 2 diabetes to metformin alone, metformin plus a lifestyle intervention, or metformin plus rosiglitazone (55). The study population included youth 10 to 17 years of age with a mean diabetes duration of 7.8 months and A1C <8%. In the entire study population, treatment failure (defined as A1C ≥8% over 6 months or sustained metabolic decompensation requiring insulin therapy) occurred in 51.7% of the metformin group, 46.6% of the metformin plus lifestyle group and 38.6% of the metformin plus rosiglitazone group (metformin-rosiglitazone vs. metformin alone; p<0.006). However, there were important differences in response between genders and ethnic groups. This study demonstrated that a significant proportion of youth with type 2 diabetes requires aggressive intervention early in the course of the disease, and treatment failure is common. Serious adverse events thought to be related to study medication were uncommon over mean follow up of 3.9 years. Given the concerns raised around the long-term safety of rosiglitazone since the start of this trial, it is premature to recommend its routine use in children on the basis of this study.

A pharmacokinetic and safety study of a single injection of exenatide (GLP-1 agonist) in 13 adolescents being treated with metformin demonstrated good tolerability and improved postprandial glucose levels (59). More recently, a randomized placebo-controlled trial of liraglutide (GLP-1 agonist) in youth with type 2 diabetes already being treated with diet/exercise alone or metformin was completed. This small study of 14 liraglutide-treated vs. 7 placebo-treated subjects provided preliminary evidence that liraglutide was well tolerated in youth with type 2 diabetes, with safety, tolerability and pharmacokinetic profiles similar to profiles in adults (60).

The experience of bariatric surgery in adolescents with type 2 diabetes is limited to several small case series with follow up ranging from 1 to 5 years. Type 2 diabetes remission rates were reported to range from 68% to 100% following vertical sleeve gastrectomy and from 79% to 94% following Roux-en-Y gastric bypass (61). While these remission rates are high, the potential benefit must be balanced against potential risks of intra-, peri- and post-operative complications, leading to additional intra-abdominal and endoscopic procedures, as well as nutritional deficiencies (including vitamin B12, thiamine and vitamin D). Notably, relapse rates in children and adolescents are yet to be published; however, up to one-third of adults have been reported to experience relapse within 5 years of initial remission that is associated with weight regain, longer duration of diabetes and insulin use prior to surgery (61). Thus, bariatric surgery in adolescents with type 2 diabetes should be limited to appropriately selected adolescents with severe obesity and be performed only by experienced teams.

Vaccination

The recommendations for influenza and pneumococcal vaccination in Canada do not address the specific condition of type 2 diabetes in children, as there are no targeted studies evaluating the usefulness of these vaccinations in this population. However, for children with diabetes mellitus, in general, the Public Health Agency of Canada (PHAC) recommends influenza vaccination given this population's high risk of influenza-related complications or hospitalization (http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php#ii5) (62), as well as pneumococcal vaccination citing an increased risk for invasive pneumococcal disease (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php#tab1) (63). Some children with type 2 diabetes may also have other factors (e.g. Indigenous heritage) that may place them at higher risk of increased influenza- and pneumococcal-related morbidity (62–65).

Complications

Youth with type 2 diabetes appear to be at significantly higher risk of developing earlier and severe microvascular and cardiovascular (CV) disease compared to youth with type 1 diabetes (66–70). Clinical factors identified in 1 study to be associated with the development of complications included older age at diagnosis and poorer metabolic control (69).

Short-term complications of type 2 diabetes in children include DKA and HHS; 10% of Canadian youth present with DKA at the time of diagnosis (2). High mortality rates (up to 37% in one series) have been reported in youth presenting with combined DKA and HHS at onset of type 2 diabetes (71–73). The management of HHS in pediatrics often requires more aggressive fluid resuscitation with delayed insulin administration at a lower dose and careful replacement of potassium, phosphate and magnesium (74). For management of DKA, see Type 1 Diabetes in Children and Adolescents chapter, p. S234.

While neuropathy has not been described in adolescents with type 2 diabetes at diagnosis, the prevalence of diabetic peripheral neuropathy was documented to be significantly higher in youth with type 2 diabetes compared to youth with type 1 diabetes in both a pilot study among SEARCH study participants (25.7% in youth with type 2 diabetes vs. 8.2% in those with type 1 diabetes) (75) and in the more extensive follow-up study (17.7% youth with type 2 diabetes vs. 8.5% in those with type 1 diabetes) (70). Peripheral nerve abnormalities were detected in 1 in 5 youth with type 2 diabetes in 1 study, with more than half having autonomic neuropathy after a median duration of diabetes of 1.3 years (67). Table 1 summarizes

Table 1
Screening for diabetes complications and comorbidities in children with type 2 diabetes

Complication/ Comorbid condition	Indications and intervals for screening	Screening test
Neuropathy	Yearly screening commencing at diagnosis of diabetes	Questioned and examined for: • Symptoms of numbness, pain, cramps and paresthesia • Vibration sense • Light touch and ankle reflexes
Retinopathy	Yearly screening commencing at diagnosis of diabetes	• 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or • Digital fundus photography
Nephropathy	Yearly screening commencing at diagnosis of diabetes	• First morning (preferred) or random ACR • Abnormal ACR requires confirmation at least 1 month later with either a first morning ACR or timed overnight urine collection for ACR • Repeated sampling should be done every 3 to 4 months over a 6- to 12-month period to demonstrate persistence
Dyslipidemia	Screening should commence at diagnosis of diabetes and yearly thereafter	Fasting TC, HDL-C, TG, calculated LDL-C
Hypertension	At diagnosis of diabetes and every diabetes-related clinical encounter thereafter (at least twice annually)	BP measurement using appropriately sized cuff
NAFLD	Yearly screening commencing at diagnosis of diabetes	ALT and/or fatty liver on ultrasound
PCOS	Yearly clinical screening commencing at diagnosis of diabetes in pubertal females	Clinical assessment on history and physical exam for oligo/amenorrhea, acne and/or hirsutism
OSA	At baseline, and yearly clinical screening	Symptoms suggestive of obstructive sleep apnea include: snoring, apneas, morning headaches, fatigue, daytime sleepiness, nocturia and enuresis
Depression	Screening at diagnosis and yearly thereafter	Clinical assessment on history of symptoms of depression, including fatigue, depressed or irritable mood, loss of interest or pleasure, feelings of worthlessness or guilt
Binge Eating	Screening at diagnosis and yearly thereafter	Clinical assessment on history: frequency of having lost control while eating, eating unusually large amounts

ACR, albumin-to-creatinine ratio; *ALT*, alanine aminotransferase; *BP*, blood pressure; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *NAFLD*, non-alcoholic fatty liver disease; *OSA*; obstructive sleep apnea; *PCOS*, polycystic ovary syndrome; *TC*, total cholesterol; *TG*, triglycerides.

the complications and comorbidities that should be screened for in youth with type 2 diabetes.

In the TODAY study, 13.7% of participants had some form of retinopathy within 2 to 8 years of diagnosis, but none had macular edema, advanced nonproliferative retinopathy or proliferative retinopathy. Older age, longer duration of diabetes and higher mean A1C appeared to be risk factors for the development of retinopathy (76). These findings suggest that screening at diagnosis and yearly thereafter is warranted (Table 1).

Albuminuria was noted in 6.3% of TODAY study participants at baseline, and the incidence of albuminuria over 3.9 years was 10.3% (2.6% yearly, comparable to adults) (77). The only identified risk factor for albuminuria was A1C. One-third of youth with albuminuria progressed to frank proteinuria. Therefore, screening for these complications at diagnosis and yearly thereafter is recommended (Table 1).

Furthermore, Aboriginal youth in Canada are at increased risk of renal diseases that are not associated with diabetes (78). Given that the documentation of persistent albuminuria may indicate one of several possible diagnoses, including underlying primary renal disease, diabetic nephropathy or focal sclerosing glomerulosclerosis (a comorbid condition associated with obesity), referral to a pediatric nephrologist for assessment of etiology and treatment is recommended (78).

Cardiovascular complications

Children with type 2 diabetes may already display cardiac structure abnormalities. In the TODAY study, 8.1% of the 455 participants having undergone cardiac echography had increased left ventricular (LV) wall thickness, 4.5% had increased LV mass and 3.6% had both (79). Changes in LV architecture were associated with obesity and higher systolic BP (as in the population without diabetes). In addition, baseline A1C was associated with both LV wall thickness and LV mass. In the absence of longitudinal data on the significance of these changes, it would be premature to recommend routine echocardiography. Nonetheless, adults with early-onset type 2 diabetes display a markedly increased risk for cardiovascular disease (CVD), with high rates of ischemic heart disease (12.6%), stroke (4.3%) and death (11%), as early as in their 40's (80). It has been estimated that the average life expectancy of individuals with early onset type 2 diabetes may be reduced by 15 years (81). Thus, children with type 2 diabetes display abnormalities in early markers of CVD and are at significantly increased CV risk as they enter adulthood, suggesting that efforts to minimize established CV factors (e.g. smoking, inactivity) must be promoted in this vulnerable population.

Comorbid Conditions

In the TODAY study, 4.5% of adolescents with recently diagnosed type 2 diabetes had elevated low-density lipoprotein cholesterol (LDL-C) or were on lipid-lowering drugs at diagnosis, and this rose to 10.7% by 36 months (82). Despite having a rigorous study protocol for the management of dyslipidemia, only 21% of those treated reached study target LDL-C levels (LDL C <2.6 mmol/L); LDL-C levels rose with A1C, independent of treatment group. Intensive healthy behaviour interventions may be beneficial to triglycerides (TG), irrespective of A1C (82). Thus, screening for dyslipidemia at diagnosis and yearly thereafter is recommended (Table 1). In children with familial dyslipidemia and a positive family history of early CV events, a statin should be started if the LDL-C level remains >4.1 mmol/L after a 3- to 6-month trial of dietary intervention (83).

In the TODAY study, the prevalence of hypertension at baseline was 11.6%, and increased to 33.8% after 3.9 years of follow up (77).

While being male, having a higher BMI and older age at baseline were associated with the development of hypertension, A1C and race/ethnicity were not. Notably, males had 87% higher risk of developing hypertension compared to females (77). Of 205 participants in the TODAY study started on lisinopril for hypertension and/or microalbuminuria, 38.5% required the maximum dose, and over one-third required additional medications. This would suggest that management of hypertension in these youth may be challenging and referral to a pediatric nephrologist should be considered. For further details and discussion on the treatment of dyslipidemia and hypertension, see Type 1 Diabetes in Children and Adolescents chapter, p. S234.

Since 95% of adolescents with type 2 diabetes present with obesity and 73% have clinical evidence of insulin resistance as manifested by acanthosis nigricans (2), surveillance should occur for comorbid conditions associated with insulin resistance, including polycystic ovary syndrome (PCOS) (2) and non-alcoholic fatty liver disease (NAFLD) (84) (Table 1). In a Canadian national surveillance study, PCOS was reported in 12.1% and NAFLD in 22.2% of children and youth at diagnosis of type 2 diabetes (2). While this study defined NAFLD as alanine aminotransferase (ALT) >3x the upper limit of normal or fatty liver on ultrasound, the definition of NAFLD is somewhat controversial, with no consensus on threshold values of ALT or what is the optimal method to identify NAFLD (85).

The prevalence of obstructive sleep apnea (OSA) in youth with type 2 diabetes remains uncertain; however, the prevalence among youth with obesity is reported to be 19% to 61% (86). A small study among youth with type 2 diabetes suggests that the prevalence may be even higher in this population than in obese youth without diabetes (87). Given the deleterious association between OSA and cardiometabolic health in adults (88), it would be prudent to clinically screen for it in youth with type 2 diabetes at diagnosis, and regularly thereafter (Table 1). Indeed, the prevalence of OSA in adults with type 2 diabetes has been reported to be above 85%. Children with symptoms suggestive of OSA should be referred to a sleep specialist for evaluation.

In the TODAY study, 14.8% of participants reported clinically significant depressive symptoms, with females more frequently affected than males (89). There were no differences in the prevalence of depressive symptoms across ethnic groups. Depression scores were inversely related to quality of life (89). Within the TODAY study, 6% of 678 respondents were classified as binge eaters (defined as 4 or more episodes of binge eating in the past month), with 24% being subclinical binge eaters (defined as 1 to 3 episodes of binge eating in the past month). Clinical binge eaters had higher BMI z-scores and percentage overweight compared with subclinical binge eaters and nonovereaters, and had greater global eating, weight and shape concerns (90). They also had more depressive symptoms and lower quality of life. There were no noted differences in the prevalence of binge eating across age, sex, race or glycemic control (90). Depressive symptoms appear to be associated with poor adherence to diabetes treatment (91,92). Given these data, we recommend screening at baseline and regularly thereafter for symptoms of depression or binge eating (Table 1), and referral to a pediatric mental health professional if symptoms are identified (see Diabetes and Mental Health chapter, p.S130).

RECOMMENDATIONS

1. All children should receive guidance promoting healthy eating, limiting sugar-sweetened beverage intake [Grade C, Level 3 (9,13,15)], limiting screen time (16), improving sleep quantity and quality, decreasing sedentary behaviours and increasing both light and vigorous physical activity [Grade C, Level 3 (10,11)] to prevent type 2 diabetes.
2. Children with obesity should receive intensive healthy behaviour interventions that incorporate family-oriented counselling and behaviour therapy to reduce the risk of diabetes [Grade D, Level 4 (9)].
3. Screening for type 2 diabetes should be considered every 2 years using a combination of an A1C and a FPG or random plasma glucose in children and adolescents with any of the following conditions:
   a. ≥3 risk factors in nonpubertal children beginning at 8 years of age or ≥2 risk factors in pubertal children [Grade D, Consensus]. Risk factors include:
      i. Obesity (BMI ≥95th percentile for age and gender) [Grade D, Level 4 (2)]
      ii. Member of a high-risk ethnic group (e.g. African, Arab, Asian, Hispanic, Indigenous or South Asian descent) [Grade D, Level 4 (2)]
      iii. First-degree relative with type 2 diabetes and/or exposure to hyperglycemia in utero [Grade D, Level 4 (2)]
      iv. Signs or symptoms of insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, NAFLD [ALT >3X upper limit of normal or fatty liver on ultrasound]) [Grade D, Level 4 (2)]
   b. PCOS [Grade D, Level 4 (2)]
   c. IFG and/or IGT [Grade D, Level 4 (23)]
   d. Use of atypical antipsychotic medications [Grade C, Level 3 (31–33)]
4. If there is a discrepancy between the A1C and FPG or random plasma glucose, testing may be repeated or a 2-hour OGTT (1.75 g/kg; maximum 75 g) may be performed [Grade B, Level 2 (38)].
5. Starting at the time of diagnosis of type 2 diabetes, all children should receive ongoing intensive counselling, including healthy behaviour interventions, from an interprofessional pediatric health-care team that includes either a pediatric endocrinologist or pediatrician with diabetes expertise, diabetes educator and mental health professional [Grade D, Consensus].
6. Regular physical activity, consisting of ≥60 minutes of moderate-to-vigorous physical activity daily, should be recommended to all children with type 2 diabetes [Grade B, Level 2 (93)].
7. The target A1C for most children with type 2 diabetes should be ≤7.0% [Grade D, Consensus].
8. In children with type 2 diabetes and A1C ≥9.0% and in those with severe metabolic decompensation (e.g. DKA), insulin therapy should be initiated but may be successfully weaned once glycemic targets are achieved [Grade D, Level 4 (56)]. Metformin should generally be started at the same time as insulin unless acidosis is present [Grade B, Level 2 (19)].
9. In children with type 2 diabetes who are metabolically stable (A1C <9.0% and no/minimal symptoms), metformin should be initiated in conjunction with healthy behaviour interventions [Grade D, Consensus]. If glycemic targets are not achieved within 3–6 months from diagnosis, then basal insulin should be initiated [Grade D, Consensus]. If targets are still not achieved on a combination of metformin and basal insulin, then prandial insulin should be initiated [Grade D, Consensus].
10. Children with type 2 diabetes should be screened for neuropathy at diagnosis [Grade D, Consensus] and annually thereafter [Grade D, Consensus].
11. Children with type 2 diabetes should be screened at diagnosis for retinopathy [Grade D, Consensus] and yearly thereafter [Grade B, Level 2 (76)].
12. Children with type 2 diabetes should be screened for chronic kidney disease at diagnosis [Grade B, Level 2 (77)] and yearly thereafter [Grade D, Consensus] with a first morning urine ACR (preferred) [Grade B, Level 2 (94)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (95)] at least 1 month later with a first morning ACR or timed, overnight urine collection for albumin excretion rate (AER) [Grade D, Consensus]. Albuminuria (ACR >2.5 mg/mmol; AER >20 mcg/min) should not be diagnosed unless it is persistent, as demonstrated by 2 consecutive first morning ACR or timed collections obtained at 3- to 4-month intervals over a 6- to 12-month period [Grade D, Consensus].
13. Children with type 2 diabetes with persistent albuminuria should be referred to a pediatric nephrologist for assessment of etiology and treatment [Grade D, Level 4 (78)].
14. Children with type 2 diabetes should have a fasting lipid profile measured at diagnosis of diabetes and yearly thereafter [Grade B, Level 2 (82)].

15. Children with type 2 diabetes should be screened for hypertension beginning at diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least biannually) [Grade B, Level 2 (77)].

16. Children with type 2 diabetes should be screened at diagnosis for comorbid conditions associated with insulin resistance, including NAFLD [Grade D, Level 4 (2,84)], OSA [Grade D, Level 4, (87)] and PCOS in pubertal females [Grade D, Level 4 (2)], and yearly thereafter as clinically indicated [Grade D, Consensus].

17. Children with type 2 diabetes should be screened at diagnosis for depression and disordered eating (in particular binge eating) and at every diabetes-related clinical encounter thereafter (at least biannually) [Grade B, Level 2 (89,90)].

Abbreviations:
A1C, glycated hemoglobin; *ACR*, albumin-to-creatinine ratio; *ALT*, alanine aminotransferase; *BMI*, body mass index; *CVD*, cardiovascular disease; *DHC*, diabetes health-care team; *DKA*, diabetic ketoacidosis; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *HDL-C*, high-density lipoprotein cholesterol; *HHS*, hyperglycemic hyperosmolar state; *LDL-C*, low-density lipoprotein cholesterol; *NAFLD*, nonalcoholic fatty liver disease; *OGTT*, oral glucose tolerance test; *PCOS*, polycystic ovary syndrome.

Other Relevant Guidelines

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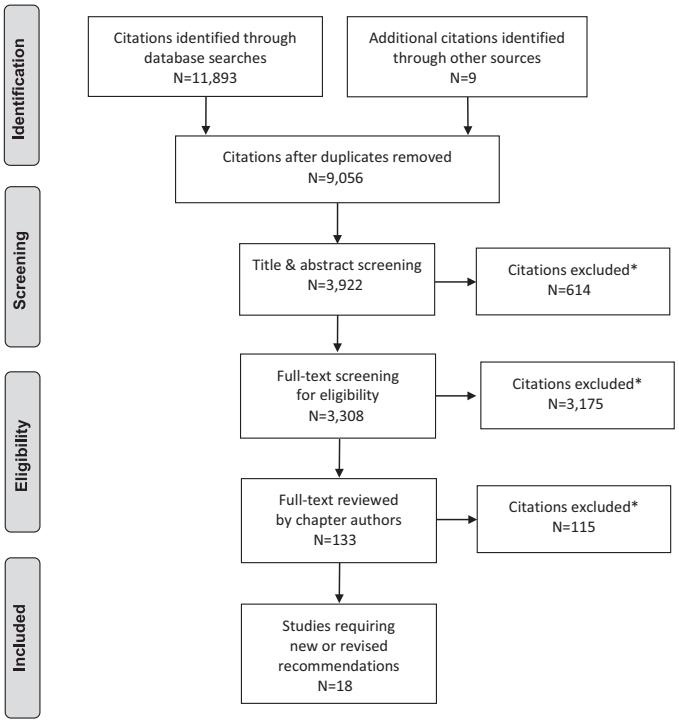
Literature Review Flow Diagram for Chapter 35: Type 2 Diabetes in Children and Adolescents



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (96).

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2018 Clinical Practice Guidelines

Diabetes and Pregnancy

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

Pre-Existing Diabetes

Preconception and During Pregnancy

- All women with pre-existing type 1 or type 2 diabetes should receive preconception care to optimize glycemic control, assess for complications, review medications and begin folic acid supplementation.
- Effective contraception should be provided until the woman is ready for pregnancy.
- Care by an interprofessional diabetes health-care team composed of a diabetes nurse educator, dietitian, obstetrician and endocrinologist/internist with expertise in diabetes, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with pre-existing type 1 and type 2 diabetes.
- Women should aim for a glycated hemoglobin (A1C) of ≤7.0% (ideally ≤6.5% if possible) when planning pregnancy, or ≤6.5% (ideally ≤6.1% if possible) during pregnancy.
- Women should consider the use of the continuous glucose monitor during pregnancy to improve glycemic control and neonatal outcomes.

Postpartum

- All women should be given information regarding the benefits of breastfeeding, effective birth control and the importance of planning another pregnancy.

Gestational Diabetes Mellitus

During Pregnancy

- Untreated gestational diabetes leads to increased maternal and perinatal morbidity. Treatment reduces these adverse pregnancy outcomes.
- In women at high risk of undiagnosed type 2 diabetes, early screening (<20 weeks) with an A1C should be done to identify women with potentially overt diabetes to guide fetal surveillance and early maternal treatment, including self-monitoring of blood glucose, interventions that promote healthy behaviours and healthy weight gain.
- The diagnostic criteria for gestational diabetes (GDM) remain controversial; however, these guidelines identify a "preferred" and an "alternate" screening approach. The preferred approach is an initial 50 g glucose challenge test, followed, if abnormal, with a 75 g oral glucose tolerance test. A diagnosis of GDM is made if one plasma glucose value is abnormal (i.e. fasting ≥5.3 mmol/L, 1 hour ≥10.6 mmol/L, 2 hours ≥9.0 mmol/L). The alternate approach is a 1-step approach of a 75 g oral glucose tolerance test. A diagnosis of GDM is made if one plasma glucose value is abnormal (i.e. fasting ≥5.1 mmol/L, 1 hour ≥10.0 mmol/L, 2 hours ≥8.5 mmol/L).
- First-line therapy consists of diet and physical activity. If glycemic targets are not met, insulin or metformin can then be used.

Postpartum

- Women with gestational diabetes should be encouraged to breastfeed immediately after birth and for a minimum of 4 months to prevent neonatal hypoglycemia, childhood obesity, and diabetes for both the mother and child.
- Women should be screened for diabetes between 6 weeks and 6 months postpartum, with a 75 g oral glucose tolerance test and be given ongoing education regarding strategies to reduce the risk of developing type 2 diabetes.

KEY MESSAGES FOR WOMEN WITH DIABETES WHO ARE PREGNANT OR PLANNING A PREGNANCY

Pre-Existing Diabetes

- The key to a healthy pregnancy for a woman with diabetes is keeping blood glucose levels in the target range—both before she is pregnant and during her pregnancy.
- Poorly controlled diabetes in a pregnant woman with type 1 or type 2 diabetes increases her risk of miscarrying, having a baby born with a malformation and having a stillborn.
- Women with type 1 or type 2 diabetes should discuss pregnancy plans with their diabetes health-care team to:
  - Review blood glucose targets
  - Assess general health and status of any diabetes-related complications
  - Aim for optimal weight and, if overweight, start weight loss before pregnancy with healthy eating
  - Review medications
  - Start folic acid supplementation (1.0 mg daily)
  - Ensure appropriate vaccinations have occurred.

Gestational Diabetes

- Between 3% to 20% of pregnant women develop gestational diabetes, depending on their risk factors
- Risk Factors include:
  - Being:
    - 35 years of age or older
    - from a high-risk group (African, Arab, Asian, Hispanic, Indigenous, or South Asian)
  - Using:
    - Corticosteroid medication
  - Having:
    - Obesity (a body mass index greater than or equal to 30 kg/m^2)
    - Prediabetes
    - Gestational diabetes in a previous pregnancy
    - Given birth to a baby that weighed more than 4 kg
    - A parent, brother or sister with type 2 diabetes
    - Polycystic ovary syndrome or acanthosis nigricans (darkened patches of skin).
- All pregnant women without known pre-existing diabetes should be screened for gestational diabetes between 24 to 28 weeks of pregnancy
- If you were diagnosed with gestational diabetes during your pregnancy, it is important to:
  - Breastfeed immediately after birth and for a minimum of 4 months in order to prevent hypoglycemia in your newborn, obesity in childhood, and diabetes for both you and your child

Conflict of interest statements can be found on page S274.

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- Reduce your weight, targeting a normal body mass index in order to reduce your risk of gestational diabetes in the next pregnancy and developing type 2 diabetes
- Be screened for type 2 diabetes after your pregnancy:
  - within 6 weeks to 6 months of giving birth
  - before planning another pregnancy
  - every 3 years (or more often depending on your risk factors).

Introduction

This chapter discusses pregnancy in both pre-existing diabetes (type 1 and type 2 diabetes diagnosed prior to pregnancy), overt diabetes diagnosed early in pregnancy and gestational diabetes (GDM or glucose intolerance first recognized in pregnancy). Some management principles are common to all types of diabetes.

Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy

The term "pre-existing diabetes in pregnancy" refers to diabetes diagnosed before pregnancy. The prevalence of pre-existing diabetes has increased in the past decade (1) primarily as a result of the increase in type 2 diabetes (2). Studies of women with pre-existing diabetes show higher rates of complications compared to the general population, including perinatal mortality, congenital malformations, hypertension, preterm delivery, large-for-gestational-age (LGA) infants, caesarean delivery and other neonatal morbidities (1,3–5).

Preconception care

Preconception care improves maternal and fetal outcomes in women with pre-existing diabetes. This involves educating women about the importance of optimal glycemic control prior to pregnancy, discontinuing potentially harmful medications and achieving a health body weight. Hyperglycemia is teratogenic and if glycemic control is poor in the first few weeks of conception, the risk of congenital anomalies is increased. Women with diabetes should be helped to achieve optimal glycemic control preconception as this is associated with a reduction of congenital anomalies by 70% (6–9). However, even women who achieve a glycated hemoglobin (A1C) ≤7.0% preconception have an increased risk of complications compared to the general population. This may be caused, in part, by maternal obesity, especially in women with type 2 diabetes (10–13).

Preconception care should also include advice regarding folic acid supplementation. In 1 case-control study in the United States, women with diabetes who did not take folic acid containing vitamins were at a 3-fold higher rate of congenital anomalies compared to women with diabetes who did (14). There are no intervention trials to support folic acid doses greater than 1 mg for women with diabetes. Obesity, which is more common in women with type 2 diabetes, is associated with lower serum folate levels for the same intake, lower intake of folate rich foods and increased risk of neural tube defects independent of glycemic control (15–17). A higher dose of folic acid may be considered in women with obesity, although there is no clinical evidence that this higher dose reduces congenital anomalies. Measurement of red blood cell (RBC) folate may also be useful to guide adjustment of folic acid dosage in women with obesity or women who have had bariatric surgery.

A multifaceted preconception program that included patient information specialized clinics, electronic health records, online resources and local guidelines, increased folic acid use by 26%, improved glycemic control and decreased the risk of congenital malformations from 5% to 1.8% (9). Although receiving care at an interprofessional preconception clinic has been shown to be associated with improved pregnancy outcomes, approximately 50% of women do not receive such care (18,19). The following factors are associated with women with pre-existing diabetes being less likely to receive preconception care: overweight; younger age; smoking history; lower socioeconomic status; lower health literacy and/or poor relationship with their health-care provider (7,20–22). Additionally, some studies have shown that women with type 2 diabetes are less likely to receive preconception care compared to women with type 1 diabetes (19,23).

Assessment and management of complications

Retinopathy. Women with type 1 (24,25) and type 2 diabetes (26) should ideally have ophthalmological assessments before conception, during the first trimester, as needed during pregnancy, and within the first year postpartum (27,28). The risk of progression of retinopathy is increased with poor glycemic control during pregnancy, and progression may occur for up to 1 year postpartum (25,27). Additional risk factors for retinopathy progression include: chronic and pregnancy-induced hypertension, preeclampsia, more severe pre-existing diabetic retinopathy (24,29–31), and a greater decrease in A1C between the first and third trimester of pregnancy (32). Closer retinal surveillance is recommended for women with more severe pre-existing retinopathy, those with poor glycemic control or women with greater reductions in A1C during pregnancy (27,33). Laser photocoagulation for severe nonproliferative or proliferative retinopathy prior to pregnancy reduces the risk of visual impairment in pregnancy (34); if not performed prior to pregnancy, it is still considered safe to receive during pregnancy.

There is insufficient evidence to confirm safety or harm from the use of intravitreal antivascular endothelial growth factor (anti-VEGF) injections for diabetic macular edema or proliferative diabetic retinopathy during pregnancy (35). Potential side effects include hypertension, proteinuria, defective embryogenesis and fetal loss (36,37). It is not known if these medications cross the placenta or if they are secreted in breastmilk. Gestational timing of exposure needs to be considered in situations where potential benefit to the woman justifies the potential fetal risk. Until more safety information is available, we support the recommendations of others: a) to ensure a negative pregnancy test and contraception use during intravitreal anti-VEGF therapy, and b) to consider delaying conception for 3 months after the last intravitreal injection (38,39). Intravitreal anti-VEGF therapy in pregnancy should be avoided especially in the first trimester. Second and third trimester use should occur only if absolutely necessary after discussion of the potential risks and benefits. Diabetic macular edema may often regress after pregnancy without specific therapy. Data are lacking to guide treatment recommendations for diabetic macular edema during pregnancy.

One retrospective study of 193 women with type 1 diabetes, 63 with an active second-stage delivery (3 with proliferative diabetic retinopathy) found no impact of expulsive efforts in the active second stage of labour on retinopathy progression in women with stable retinopathy (40). Data from the Diabetes Control and Complications Trial (DCCT) has suggested that pregnancy does not affect the long-term outcome of mild-to-moderate retinopathy (27). More recently, preeclampsia and pregnancy-induced hypertension in women with type 1 diabetes has been shown to be associated with an increased risk of severe diabetic retinopathy later in life (41).

Hypertension. Women may have pre-existing hypertension or develop hypertension/preeclampsia during pregnancy. Women with type 1 and type 2 diabetes have a 40% to 45% incidence of hypertension complicating pregnancy (31). A systematic review of risk factors for preeclampsia demonstrated a 3.7 risk (relative risk [RR] 3.1 to 4.3) for the development of preeclampsia in women with pre-existing diabetes (42). Type 1 diabetes is more often associated with preeclampsia whereas type 2 diabetes is more often associated with chronic hypertension. In the general population, the risk of preeclampsia is highest in nulliparous women and lower in multiparous women. However, in women with type 1 diabetes, the risk of preeclampsia is similar in nulliparous and multiparous women (43). Other risk factors for hypertension, such as poor glycemic control in early pregnancy, are potentially modifiable. Some studies (44,45), but not all (46), have found that increased urinary protein excretion in early pregnancy is associated with an increased risk of hypertension.

Any type and degree of hypertension is associated with adverse outcomes. A large randomized controlled trial in pregnant women with nonproteinuric pre-existing or gestational hypertension (that included women with GDM) showed that targeting a diastolic blood pressure (BP) of 85 mmHg vs. 100 mmHg reduced neonatal respiratory complications, rates of severe maternal hypertension (i.e. >160/110 mmHg) and did not increase the incidence of small for gestational age (SGA) (47). Finally, a number of antihypertensive medications are safe and effective in pregnancy, including calcium channel blockers, labetalol and methyldopa.

Although there are no intervention trials for ASA prophylaxis for the prevention of preeclampsia specific to women with pre-existing diabetes, ASA prophylaxis started between 12 to 16 weeks of gestation is likely to be beneficial, given the evidence of benefit in other high-risk populations, (48).

Based on a meta-analysis and systematic review, calcium supplementation (of at least 1,000 mg/day) in high-risk populations, especially in those with low dietary calcium intake, may reduce preeclampsia rates by up to 40%, although evidence is limited (49).

Chronic kidney disease. Prior to conception, women should be screened for chronic kidney disease (CKD). Albuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications (50–55). An estimated glomerular filtration rate (eGFR) should be used prior to pregnancy to determine risk of adverse outcomes. In 1 small study, women with poorer mean preconception creatinine clearance (CrCl) of 61 mL/min/1.73 m^2 (range 37 to 73) showed a 36% lower creatinine clearance (CrCl) 3 months postpartum, whereas in women with a mean preconception CrCl of 80 mL/min/1.73 m^2 (range 70 to 93), no deterioration in renal function was observed (56). However, inadequate BP control in pregnancy may account for this observed difference in this study.

During pregnancy, serum creatinine (not eGFR) should be used, as eGFR will underestimate GFR in pregnancy (57,58). Proteinuria increases during pregnancy, but, in women with a normal GFR, pregnancy has no adverse effects on long-term renal function as long as BP and blood glucose (BG) are well controlled (50–53,56,59,60). One small series found that women with serum creatinine >124 µmol/L at pregnancy onset had a greater than 40% chance of accelerated progression of diabetic nephropathy as a result of pregnancy (61). First trimester BP elevations and protein excretion are associated with delivery before 37 weeks, usually due to preeclampsia (62). Small cohort studies have suggested that antihypertensive therapy for BP >135/85 mmHg in women with diabetes and albuminuria during pregnancy may reduce the risk of preeclampsia and preterm delivery without adversely impacting other pregnancy outcomes (60,63,64).

There is conflicting information on whether first-trimester exposure to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is associated with an increased risk of congenital malformations (65,66). A meta-analysis, limited by small study size (n=786), demonstrated a significant risk ratio (relative risk [RR] 1.78, 95% confidence interval [CI] 1.07–2.94) of increased anomalies in infants exposed to first-trimester ACE inhibitors and ARBs compared to the general population (67). However, when the group exposed to ACE inhibitor/ARB was compared to a group of women who were exposed to other antihypertensives used in pregnancies, they were both associated with malformations with no statistically significant difference. Fetal exposure in the second and third trimesters is clearly associated with a fetal renin angiotensin aldosterone system (RAAS) blockade syndrome, which includes renal failure, oligohydramnios, hypotension, intrauterine growth restriction and death (68). The decision to discontinue an ACE inhibitor or ARB prior to pregnancy should be discussed with the woman and may depend on the indication for use and availability of an effective alternative medication. However, once a woman is pregnant, ACE inhibitors and ARBs should be discontinued.

Painful peripheral neuropathy management. As with all medications used in pregnancy, benefits need to be weighed against risk. In the relatively small number of reported pregnancies in which women were exposed to first trimester gabapentin monotherapy (n=294), no increased risk of congenital malformations was found (69,70). However, neonatal gabapentin withdrawal has been described with maternal oral gabapentin 600 mg 3 times daily throughout pregnancy (69).

Cardiovascular disease. Although rare, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. Myocardial infarct (MI) in pregnancy is associated with poor maternal and fetal outcomes (71,72). Women with known CVD should be evaluated and counselled about the significant risks associated with pregnancy. As well, statins and/or fibrates should be discontinued prior to pregnancy as they are not recommended for use during pregnancy.

Management

Care by an interprofessional diabetes health-care (DHC) team composed of diabetes nurse educators, dietitians, obstetricians and endocrinologists/internists with expertise in diabetes, both preconception and during pregnancy, has been shown to minimize maternal and fetal risks in women with diabetes (73–76) (see Organization of Care chapter, p. S27). An early working relationship should be established between the woman and the DHC team to optimize care, facilitate the planning of pregnancy, ensure adequate self-care practices and to discuss the need for social support during pregnancy.

Targets of glycemic control

Elevated BG levels have adverse effects on the fetus throughout pregnancy. At conception and during the first trimester, hyperglycemia increases the risk of fetal malformations and intrauterine fetal demise (77). Later in pregnancy, it increases the risk of macrosomia, fetal and infant death (77) as well as metabolic and obstetrical complications at birth (78,79). As a result, meticulous glycemic control throughout pregnancy is required for optimal maternal and fetal outcomes.

An important first step in achieving optimal glycemic control is to set target BG levels (74,79). However, optimal targets for fasting, preprandial and postprandial BG levels in women with pre-existing diabetes have not been examined in randomized controlled trials; and a variety of BG targets are used in clinical practice.

Older studies confirm that the lower the mean BG, the better the outcome, with some suggesting a target mean BG <6.7 mmol/L and, others, a mean <6.9 mmol/L. A fasting BG (FBG) target <5.9 mmol/L is still associated with a 29% macrosomia rate (74,80,81). Recent retrospective data demonstrated that a mean A1C ≥6.0% in pregnant women with type 2 diabetes was associated with increased risk of neonatal complications (preterm birth, neonatal intensive care unit [NICU] admission, neonatal hypoglycemia and jaundice) compared to women with an A1C <6.0% (82). In women with type 1 diabetes and good glycemic control during pregnancy with an A1C of 4.5% to 7.0%, there is still a linear relationship between third trimester A1C and risk of macrosomia (83).

In the absence of comparative studies of specific BG targets for women with pre-existing diabetes, use of the mean BG plus 2 standard deviation (SD) of pregnant women without diabetes appears to be appropriate. This translates into BG targets of fasting and preprandial <5.3 mmol/L; 1 hour postprandial <7.5 mmol/L and 2 hours postprandial <6.7 mmol/L (84). Studies in gestational (GDM) indicate a 1 hour postprandial target <7.8 mmol/L is associated with good pregnancy outcomes (85–89); thus, harmonizing the 1 hour target <7.8 mmol/L is reasonable.

An A1C <6.5% should be strived for in all women with pre-existing diabetes during pregnancy; however, given the slightly increased risk of stillbirth in women with an A1C >6.1% (77), ideally a target A1C ≤6.1% should be sought by the third trimester of pregnancy, if it can be achieved safely.

Definition of hypoglycemia in pregnancy

Hypoglycemia is traditionally defined as a BG <4.0 mmol/L; however, as demonstrated by a group who compared continuous glucose monitoring (CGM) with glucose levels from nonpregnant and pregnant women, BG levels are lower during pregnancy by a factor of 20% (90). By consensus, the American Diabetes Association and Endocrine Society Working Group defined hypoglycemia during pregnancy as a level <3.3 mmol/L (91). However, since the hypoglycemia level is often individualized to each person with diabetes, with consideration of symptoms, therapy, medical condition and associated risk; the official lower limit of BG level during pregnancy is difficult to clearly establish. Overall, it is understood that pregnant women have lower BG values that can be judged as normal even if below the traditional level of 4.0 mmol/L. However, women receiving insulin therapy should maintain BG values >3.7 mmol/L to avoid repeated hypoglycemia.

Hypoglycemia is generally considered to be without risk for the fetus, as demonstrated in women with pre-existing diabetes (79,92–94), as long as it is not sustained and maternal loss of consciousness, convulsion, and fall or trauma is avoided during the episode (91). However, repeated hypoglycemia and associated loss of glycemic control have been associated with macrosomia (95).

The limiting factor when targeting euglycemia in women with pre-existing diabetes is the increased risk of hypoglycemia during pregnancy, particularly in the first trimester (96–100), for both type 1 and type 2 diabetes (79). Up to 71% of pregnant women with pre-existing diabetes may experience severe hypoglycemia, with the major predictors being a history of severe hypoglycemia in the 1-year period preceding pregnancy, diabetes duration >10 years and hypoglycemic unawareness (96–100). The latter may relate, in part, to the loss of counterregulatory hormones reported in women with pre-existing diabetes during pregnancy, particularly growth hormone and epinephrine (95,101–103). This risk of hypoglycemia may be ameliorated if efforts are made to achieve good glycemic control preconception and by the use of analogue insulins (100,104,105) (see Hypoglycemia chapter, p. S104). Health-care providers should ensure that pregnant women with diabetes: a) have a glucagon kit; b) are advised regarding effective interventions if a severe hypoglycemic event occurs; and c) are encouraged to inform close relatives and co-workers of this increased risk, especially in the first and early second trimester.

Monitoring

Frequent self-monitoring of blood glucose (SMBG) in pregnant women with type 1 diabetes is essential during pregnancy in order to achieve the glycemic control associated with better outcomes (80). Preprandial testing (to guide mealtime insulin dose adjustment) and postprandial testing (to meet postprandial targets) are associated with less macrosomia in observational studies and reduced preeclampsia (81,106,107). Due to the increased risk of nocturnal hypoglycemia with any intensive insulin therapy, SMBG during the night is often necessary in pregnant women with diabetes receiving insulin (108). SMBG 4 to 7 times per day is also recommended for pregnant women with type 2 diabetes (i.e. fasting, preprandial and 1 or 2 hours postprandially) to achieve good glycemic control.

CGM may help identify periods of hyper- or hypoglycemia (109,110) and can confirm glycemic variability, especially in women with type 1 diabetes (111). Evidence for the use of CGM to improve glycemic control, and maternal and fetal outcomes is conflicting. One study using blinded, intermittent CGM with review of results with a clinician showed that CGM improved A1C and rates of macrosomia compared to standard care (109). However, a study of intermittent real-time CGM did not demonstrate benefit (112). Finally, a study examining CGM use to prevent episodes of severe hypoglycemia early in pregnancy in women with a history of episodes in the year prior to pregnancy did not demonstrate benefit. The Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy (CONCEPTT) trial randomized 325 women (215 pregnant and 110 planning pregnancy) to capillary blood glucose (CBG) monitoring with CGM or without. Pregnant CGM users spent more time in target (68% vs. 61%, p=0.0034) and less time hyperglycemic (27% vs. 32%, p=0.0279) than did pregnant control participants, with comparable severe hypoglycemic episodes and time spent hypoglycemic. Neonatal health outcomes were significantly improved, with lower incidence of LGA (OR 0.51, 95% CI 0.28–0.90, p=0.021), fewer NICU admissions lasting more than 24 h (OR 0.48, 95% CI 0.26–0.86, p=0.0157), and fewer incidences of neonatal hypoglycemia (OR 0.45; 95% CI 0.22–0.89, p=0.025. No benefit was observed for women planning a pregnancy (113). Whether closed-loop systems will be beneficial for use in pregnancy remains to be seen (114). One study of pregnant women with type 1 diabetes showed overnight closed-loop therapy resulted in better glycemic control than sensor-augmented pump therapy (115).

Women with pre-existing diabetes during pregnancy should have A1C levels measured during pregnancy to assist in management. A1C levels can also be helpful predictors of adverse pregnancy outcomes (116,117). The optimal frequency of A1C measurement is not known; however, testing more than the usual every 3 months may be appropriate (see Monitoring Glycemic Control chapter, p. S47).

Weight gain

Institute of Medicine (IOM) guidelines for weight gain in pregnancy were first established in 1990 based on neonatal outcomes. Results of a systematic review of studies examining the 1990 IOM recommendations for maternal weight gain in women without diabetes, showed that those who followed guidelines were more likely to have good infant birthweight and fetal growth, and decreased the amount of weight loss required postpartum (118). The IOM

revised their recommendations in 2009 due to increasing rates of obesity and to take into consideration maternal obesity; however, IOM recommendations do not take into account pre-existing medical conditions (119).

Cohort studies of various body mass index (BMI) classes of women with pre-existing diabetes showed that excessive gestational weight gain (GWG) is characterized by higher birth weight infants independent of pre-pregnancy BMI and glycemic control (120,121). The researchers suggest that aiming for the lower weight gain range based on BMI category may be useful in the management of women with pre-existing diabetes. Furthermore, prepregnancy overweight and obesity are risk factors for adverse maternal and neonatal outcomes. Findings of cohort studies with pregnant women with type 2 diabetes who had overweight or obesity showed that weight gain greater than the IOM recommendations was associated with increased macrosomia (122–124), LGA (124), adverse neonatal outcomes (123) and higher rates of caesarean deliveries (122,123). The number of women with excessive GWG in these studies ranged from 40% (122) to 70% (124). Studies investigating weight gain below the IOM guidelines in women with obesity and type 2 diabetes have produced conflicting results ranging from: no evidence of worsened perinatal outcomes (122); increased risk of SGA (123); and lower birth weight, LGA and less perinatal morbidity with no increased risk of SGA (125).

Prepregnancy BMI, glycemic control and GWG can have independent and additive effects on fetal growth. Therefore, diabetes education and management for this group of women in preconception and regularly throughout pregnancy should be inclusive of both optimal glycemic control, healthy preconception weight and weight gain through pregnancy. Until additional data on specific weight gain recommendations for women with pre-existing diabetes becomes available, these women should be advised to gain weight as per the IOM guidelines based on their prepregnancy BMI category to lower the risk of LGA, macrosomia and caesarean deliveries.

Pharmacological therapy

Insulin. Insulin therapy must be individualized and regularly adapted to the changing needs of pregnancy (126–129). Intensive insulin therapy with basal-bolus therapy or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy is recommended to achieve glycemic targets prior to pregnancy and during pregnancy. Women using CSII should be educated about the possible increased risk of diabetic ketoacidosis (DKA) in the event of insulin pump failure. However, recent studies using pumps have not demonstrated an increase in DKA compared to multiple daily injections (MDI) (130).

Rapid-acting bolus analogues (e.g. aspart, lispro) appear safe for use in pregnancy, with some studies showing improvement in postprandial glycemia and reduced maternal hypoglycemia compared to regular insulin (131–133). Although there are no studies that have examined placental transfer of aspart, lispro has been examined and does not cross the placenta except at very high doses (>50 units), similar to human insulin (134). A meta-analysis of observational studies (1561 women with pre-existing diabetes and GDM) found that lispro compared to regular insulin was associated with decreased rates of severe maternal hypoglycemia and neonatal jaundice, but increased rates of LGA infants (135). A randomized trial of 322 women with type 1 diabetes randomized to insulin aspart vs. human regular insulin, showed a trend toward reduced episodes of major hypoglycemia, with improved postprandial BG levels but similar overall glycemic control (104). In a smaller, underpowered study, perinatal outcomes were similar using insulin aspart and human insulin (136). A meta-analysis of randomized trials of 1,143 women with gestational or pre-existing diabetes assessing the use of insulin aspart or premixed biphasic insulin aspart 30 compared to human regular insulin or premixed biphasic insulin aspart during pregnancy found similar rates of caesarean section and macrosomia (135). Finally, a case series of 303 women exposed to glulisine during pregnancy showed no noted pattern of few birth defects (137). There are no data to date on faster-acting insulin aspart.

Long-acting insulin analogues, glargine and detemir, appear safe with similar maternal and fetal outcomes compared to neutral protamine hagedorn (NPH) insulin. Both glargine and detemir (138) do not cross the placenta at therapeutic doses, although glargine does cross at very high doses (139). Notably, 2 randomized trials of detemir use compared with NPH in women with type 1 diabetes showed a lowering of FBG, but similar A1C, maternal hypoglycemia, and other maternal and fetal outcomes (140); another trial found less hypoglycemia with detemir compared with NPH (141). The research evidence for glargine are more limited (cohort and case control studies); however, in a meta-analysis of cohort studies comparing glargine to NPH, maternal and fetal outcomes were similar (142) and no adverse maternal or fetal effects have been described to date. Finally, there are no benefit or harms data on the use of glargine insulin U-300, lispro insulin U-200, degludec insulin U-100 and U-200, or glargine biosimilar in pregnancy.

CSII therapy during pregnancy. While the use of CSII may be preferred by some women with type 1 diabetes, older randomized studies have not demonstrated superiority over basal-bolus regimen (132,143–146). A meta-analysis of observational studies comparing the use of CSII (with insulin analogs) to MDI found no differences in maternal or fetal outcomes (147). However, recent studies not included in the meta-analysis suggest improved glycemic control with CSII (148–150), while other studies found no difference (151). Overall, studies show no difference in maternal or fetal outcomes with CSII, but also no increase in harms, such as maternal hypoglycemia, DKA or weight gain. More randomized trials are needed with current CSII technology to better assess the utility of CSII during pregnancy.

Noninsulin antihyperglycemic agents and pregnant women with type 2 diabetes. A meta-analysis of first-trimester use of either glyburide or metformin, and a meta-analysis of metformin alone in women with polycystic ovary syndrome (PCOS) showed no increased incidence of congenital anomalies (152,153). Women with type 2 diabetes who conceive on metformin or glyburide can continue these agents until insulin is initiated. Three smaller randomized trials have examined the use of metformin in pregnant women with type 2 diabetes. The first study was a small, open-label trial in Egypt (n=90) requiring high doses of insulin with poor glycemic control randomized to receive either metformin added to insulin or usual care (154); unfortunately, the authors did not specify whether the women had GDM or type 2 diabetes. The second trial completed in the United States (n=28) involved women with type 2 diabetes randomized to metformin or insulin and showed similar glycemic control in both groups (155). Finally, the third trial completed in Pakistan (n=206) involved women with untreated type 2 diabetes randomized to receive either metformin with insulin (as necessary), or insulin alone (156). In this study, 85% of patients in the metformin group required add-on insulin, but this group experienced less maternal weight gain, less pregnancy-induced hypertension; the infants had an increased rate of small for date, less hypoglycemia and less NICU admissions >24 hours. However, given the small sample sizes in the study and other methodological challenges, the findings from these studies offer limited generalizability.

Currently, a large, double-blind randomized trial is underway to determine whether adding metformin to insulin will benefit

Table 1
Management of pregnant women with diabetes on insulin receiving betamethasone

Following the first dose of betamethasone	
Day 1	Increase the night insulin dose by 25%
Days 2 and 3	Increase all insulin doses by 40%
Day 4	Increase all insulin doses by 20%
Day 5	Increase all insulin doses by 10% to 20%
Days 6 and 7	Gradually taper insulin doses to pre-betamethasone doses

mothers with type 2 diabetes and their infants (Metformin in Women with Type 2 Diabetes in Pregnancy [MiTy] and Metformin in Women with Type 2 Diabetes in Pregnancy Kids [MiTy Kids] trials). In conclusion, some studies indicate a possible benefit to adding metformin to insulin in women with type 2 diabetes; however, due to limitations in the research, there is insufficient evidence to recommend the addition of metformin to insulin in pregnant women with type 2 diabetes.

Pregnant women with diabetes receiving steroids. In women suspected of preterm delivery, 2 doses of betamethasone is often given to aid in the maturation of the fetal lungs. The algorithm in Table 1 has been shown to prevent severe hyperglycemia, DKA and severe hypoglycemia in women with type 1 diabetes (157).

Perinatal mortality

Despite health care advances, including NICU, accurate ultrasound dating, SMBG and antenatal steroids for fetal lung maturity, perinatal mortality rates in women with pre-existing diabetes remain increased 1- to 10-fold compared to women without diabetes, and is influenced by glycemic control (1,77). In women with pre-existing diabetes, the risk of stillbirth is higher at all gestations after 32 weeks (158). Perinatal mortality is increased in pregnancies of women with pre-existing diabetes, particularly in those with poor glycemic control (159). In addition, a recent study found that peri-conception A1C >6.6% (adjusted odds ratio [aOR] 1.02), prepregnancy retinopathy (aOR 2.05), lack of prepregnancy folic acid consumption (aOR 2.52) and third-trimester A1C >6.1% (aOR 1.06) were all associated with an increased odds of fetal and infant death (77).

Significance of decreasing insulin requirements

Insulin requirements increase in pregnancy due largely to the "anti-insulin" effects of placental hormones. It has been hypothesized that a marked or rapid decrease in insulin requirements could be a harbinger of placental insufficiency. The relationship between falling insulin requirements and pregnancy outcomes has been explored in 4 retrospective studies (160–163). The 4 studies (n=481 pregnancies) comprised women with type 1 diabetes (n=366), women with type 2 diabetes (n=84), women diagnosed with overt diabetes in pregnancy (n=12) and women with insulin-requiring GDM (n=19). These studies reported decreased insulin requirements (at least 15%) occurred during the third trimester in 8% to 25% of these pregnancies. Only 2 stillbirths occurred: both in the same study of women with pre-existing diabetes (1 in a pregnancy with a >15% decrease in insulin requirements, the other in a pregnancy without a 15% decrease in insulin requirements) (160). This same study found that pregnancies with greater decreases in insulin requirements (>15%) were associated with more SGA neonates and more pre-eclampsia when compared to those that did not have at least a 15% decrease in insulin requirements, suggesting that dropping insulin requirements may be an indicator of placental insufficiency. Those with the ≥15% drop in insulin requirements compared to those without, were delivered slightly earlier at a mean of 37.7 vs. 38.3 gestational weeks. Therefore, not surprisingly, those with the greater decrease in insulin requirements compared to those without, were admitted more frequently to the NICU (23.5% vs. 1.9%, p<0.001). Although care was taken not to include the period within 5 days of antenatal steroid administration when calculating the percent fall in insulin dosing in this study, the substantially higher antenatal steroid use in the pregnancies with falling insulin requirements (31.5% vs. 5.8%, p<0.001) in those without this same fall in insulin requirement suggests that antenatal steroid use may have impacted their retrospective determination of group assignment and, ultimately, their results. However, caution is required in the interpretation of these retrospective studies since decreasing insulin requirements may impact decisions regarding timing of delivery which may, in turn, impact pregnancy outcomes.

In contrast, results from other studies found no association with decreasing insulin requirements and birthweight, and neonatal weight distribution (i.e. SGA to LGA) (161). However, 1 study observed a trend for greater LGA neonates in women with decreasing insulin requirements (162). Caution is required when interpreting the findings as researchers used differing calculation methods to indicate fall in insulin requirements or perhaps due to heterogeneity in the population of women with type 2 diabetes included in the studies. The use of advanced sonographic and fetal doppler assessment in the surveillance of the fetus at risk, as in other high-risk pregnancies, may allow further stratification of risk in this population, but the optimal indicator of feto-placental compromise, particularly in women with diabetes, remains unclear.

In summary, the impact of decreasing insulin requirements is still not certain. While fetal monitoring in this situation can provide reassurance of current fetal well-being, it should not be viewed as a substitute for a well thought out plan for timing of delivery that takes into consideration other risks for perinatal mortality, such as gestational age, maternal glycemic control (both periconception and in later pregnancy), prepregnancy retinopathy (77), maternal age, obesity and smoking history.

Obstetrical considerations in women with pre-existing diabetes and GDM

The goal of fetal surveillance and planned delivery in women with pre-existing diabetes in pregnancy is the reduction of preventable stillbirth. However, not all stillbirths can be avoided due to the fact that many stillbirths in pre-existing diabetes occur prior to 36 weeks of gestation and that in a large number of cases no obvious cause is noted (164). Despite this, it is reasonable to apply surveillance strategies to pre-existing diabetes pregnancies that are similar to those in other pregnancies at high risk of fetal complications, such as intrauterine growth restriction (IUGR), chronic hypertension, and systemic lupus erythematosis (165). Although there is no single strategy for antenatal surveillance for pre-existing diabetes pregnancies, the initiation of some form of fetal surveillance in all women with pregnancies complicated by pre-existing diabetes while applying more intensive protocols for fetal surveillance in pregnancies with additional risk factors is required. These risk factors include: evidence of poor glycemic control, prepregnancy retinopathy (77), LGA, polyhydramnios or the presence of other comorbidities or high-risk conditions (hypertension, obesity, late maternal age, IUGR, previous stillbirth). As a general rule, intensified fetal surveillance should begin at a period in gestation when intervention (i.e. delivery) is possible and acceptable to both the parents and the neonatal care providers.

For GDM, fetal surveillance and timing of delivery are more complex as there is less evidence for increased perinatal mortality in this group. This is likely due to the fact that the risk for perinatal mortality is probably limited to the subgroup of women with poor glycemic control, inclusion of women with pre-existing diabetes

in GDM cohorts, obesity and other comorbidities and the rarity of these events. However, a large retrospective cohort (166) showed an increased risk of stillbirth in women with GDM between 36 to 39 weeks of gestation (unadjusted OR 1.1–2.00). Based on the large dataset, a relative risk was calculated of expectant management compared with induction of labour, while taking into consideration both the risk of stillbirth (expectant management) and infant death (expectant management and induction of labour) and showed a significant increased risk of stillbirth with expectant management at both 39 and 40 weeks of gestation when compared with induction of labour. As the absolute risk difference was small, the number needed to deliver to prevent 1 excess perinatal death was estimated as 1,518 at 39 weeks' gestation and 1,311 at 40 weeks' gestation. However, this study is limited by unadjusted confounders, including adequacy and method of glycemic control as well as obesity, thus limiting the generalizability of the study.

There are additional potential benefits of induction of labour in diabetic pregnancies, including reduction of excess fetal growth, shoulder dystocia and caesarean section rate. One randomized controlled trial compared induction of labour with expectant management of labour at term (167). In this trial of insulin requiring GDM and pre-existing diabetes in pregnancies, expectant management after 38 weeks of gestation was associated with increased birthweight and macrosomia, but no change in caesarean section rate. A recent retrospective cohort study from Ontario supports these findings, showing a significant reduction in caesarean section rate at both 38 and 39 weeks of gestation in women with GDM who underwent induction of labour when compared with those that underwent expectant management (168). Conversely, induction of labour at 38 but not 39 weeks was associated with an increase in NICU admission. Importantly, these results remained significant after adjusting for important confounders, including parity, insulin treatment and BMI. Two recently published randomized controlled trials shed additional light on this clinical question. One study randomized women with a suspected macrosomic fetus (>95%) to either induction of labour (IOL) at 37 to 39 weeks or expectant management up until 41 weeks. Although the trial population included diet-controlled GDM (10%), the results showed that IOL resulted in an increased rate of spontaneous vaginal delivery (RR 1.14, 95% CI 1.01–1.29), a decrease in the rate of shoulder dystocia (RR 0.32 95% CI 0.12–0.85) and an increase in the rate of neonatal hyperbilirubinemia (169). A second randomized controlled trial randomized women with both diet-controlled and medically treated GDM to IOL at 38 to 38+6 weeks or expectant management until 41 weeks' gestation. The study found no difference in caesarean section rates between groups, but an increase in hyperbilirubinemia was noted in the IOL group. However, the study was underpowered and discontinued due to recruitment difficulties; thus any extrapolations from the study cannot be made (170).

In summary, there is a paucity of quality evidence to guide clinical decisions regarding optimal fetal surveillance and timing of delivery in diabetic pregnancies. Clinical identification of increased risk of stillbirth should be the target of prenatal care and lead to an individualized approach to defining the appropriate regimen of fetal surveillance and timing of delivery. In pre-existing diabetes, poorly controlled GDM or pre-existing diabetes in pregnancy associated with comorbidities, initiation of weekly assessment of fetal well-being at 34 to 36 weeks gestation is recommended. Earlier onset and/or more frequent fetal health surveillance is recommended in those at highest risk. Acceptable methods of assessment of fetal well-being near term can include the nonstress test, amniotic fluid index, biophysical profile or a combination of these. When making decisions regarding timing of delivery before 40 weeks' gestation, the benefits with regards to prevention of stillbirth and a possible decrease in the caesarean rate need to be weighed against the likely increase in neonatal complications.

Glycemic control in labour and delivery

Planning insulin management during labour and delivery is an important part of care and must be adaptable given the unpredictable combination of work of labour, dietary restrictions and need for an operative delivery. The goal is to avoid maternal hypoglycemia while preventing significant hyperglycemia which, in turn, may increase the risk of neonatal hypoglycemia (171). Options for peripartum BG control include watchful waiting until BG rises above a specified threshold (e.g. 7.0 mmol/L for type 2 diabetes or GDM), presumptive initiation of intravenous insulin infusions or continuing with CSII therapy. In a retrospective study of 161 consecutive women with type 1 diabetes, women who chose to continue on CSII during labour had better glycemic control than women using CSII during pregnancy but who chose to convert to intravenous insulin infusion during labour. There was no increase in maternal hypoglycemia, suggesting that the continuation of CSII during labour and delivery appears safe and efficacious (172). Similarly, another retrospective study found that women using CSII had excellent glycemic control without hypoglycemia (173). Observational studies comparing the use of CGM to SMBG during labour and delivery identified improved glycemic control with CGM (173,174); however, neonatal hypoglycemia was comparable between groups (172,174). Each centre should establish protocols which include BG targets, monitoring frequency, insulin regimen and intravenous glucose, based on nursing, medical and anaesthesia expertise available, and patient choice (171,172).

Postpartum care

Postpartum care in women with pre-existing diabetes should include counselling on the following issues: 1) rapid decrease in insulin needs and risk of hypoglycemia in the immediate postpartum period; 2) risk of postpartum thyroid dysfunction in the first months; 3) benefits of breastfeeding; 4) contraceptive measures and; 5) psychosocial assessment and support during this transition period.

Diabetes management and insulin sensitivity immediately postpartum. In women with type 1 and type 2 diabetes, insulin requirements decrease rapidly immediately after the delivery of the placenta (175–177). This rapid increase in insulin sensitivity is related to the drop in circulating placental hormones (hPL, HGH) and, as a result, intravenous insulin infusion or CSII basal insulin should be immediately decreased by at least 50% after delivery to avoid hypoglycemia (175,178).

In the first days postpartum, insulin requirements are generally reduced by an average of 30% to 50% of the prepregnant insulin dosage in women with type 1 diabetes (175–177). In a recent study of 44 women with type 1 diabetes (73% on pumps, 27% on MDI), postpartum total daily insulin was 34% lower than preconception total needs (0.64 to 0.39 units/kg/day postpartum) independent of insulin administration mode or infant feeding. However, a nonsignificant trend toward lower requirements in exclusively breastfeeding mothers compared to partial or full formula feeding was also noted (176). A gradual return to pre-pregnant insulin doses has been noted after 6 to 8 weeks postpartum in some studies (179,180); however, another study found persistently reduced insulin needs up to 4 months postpartum (181). In some studies, reduced insulin needs have been especially noted in women with type 1 diabetes who were breastfeeding (180,181), although this has not been universally observed (176). Nevertheless, most clinicians advise women with type 1 diabetes who are breastfeeding of the potential increased risk of hypoglycemia, especially during night breastfeeding. Thus, for women with pre-existing diabetes in pregnancy, a post-delivery plan for reduced prepregnant insulin dosages, pump settings or

noninsulin antihyperglycemic agents should be discussed with the woman and recorded before delivery.

Evidence suggests that despite good glycemic control during pregnancy, continuous weight loss, as well as substantial diabetes education and follow up during pregnancy and in the first months postpartum, glycemic control is managed less effectively by mothers with diabetes in the first year postpartum, and A1C levels gradually increase and return to the pre-pregnancy level (182,183). Postpartum A1C levels are positively associated with pre-pregnancy BMI and postpartum weight retention in type 1 diabetes (182). In addition, most women are unable to return to prepregnancy weight (183). Improved postpartum care and specific interventions for women with pre-existing diabetes should be developed to help women achieve their target weight postpartum (182,183), to improve glycemic control in the first year postpartum (183) and to increase breastfeeding rates (184).

Risk of postpartum thyroid dysfunction. Women with type 1 diabetes are at high risk for autoimmune thyroid disease and, consequently, postpartum thyroid dysfunction. The estimated incidence is as high as 44% among women of childbearing age, and 25% in the first months postpartum (185), representing a 3-fold increase compared to a population without diabetes (185,186). Screening for thyroid hormonal abnormalities during pregnancy and at approximately 3 months postpartum in women with type 1 diabetes is recommended.

Breastfeeding

Lower rate and difficulties around delayed lactation in women with diabetes. A Canadian group demonstrated that women with pre-existing diabetes were less likely to initiate breastfeeding compared with noninsulin-treated mothers with diabetes, GDM women and mothers without diabetes (184). Concordant with other studies (187,188), women with all types of diabetes in pregnancy (GDM, pre-existing, insulin-treated or noninsulin-treated) in this study had also lower rates of exclusive breastfeeding in hospital and on discharge. However, women with pre-existing diabetes were disproportionately affected and had lower rates of breastfeeding (184,189). Lower education and maternal age less than 25 years of age were risk factors associated for lower rates of breastfeeding and exclusive breastfeeding postpartum (184).

Women with pre-existing diabetes tend to have delayed milk production. There is a greater delay in lactation onset in mothers with type 1 diabetes who had poor glycemic control (190). Women with type 1 diabetes also discontinue breastfeeding at a higher rate during the first week postpartum (191–193). Overall, women with any form of diabetes during pregnancy have more nursing difficulties with lower milk supply than women without diabetes (194). However, once established, lactation persists and duration is similar in mothers with and without diabetes (190,195).

There are several pathophysiologic and behavioural explanations for lower breastfeeding rates in women with diabetes. Poor glycemic control, insulin resistance, obesity and impaired bonding between mother and child caused by obstetrical complications (such as NICU admission, prematurity, caesarean section) are the major factors associated with delayed lactation (196). It has been demonstrated that ideal glucose and insulin levels are necessary for lactation (197). Good glycemic control enhances maternal serum and milk prolactin concentrations and decreases the delay in the establishment of lactation that has been observed in mothers with type 1 diabetes (190,198). Maternal obesity has also been correlated with delayed onset of lactogenesis II (>72 hours) postpartum, partly related to the fact that it can alter spontaneous release of prolactin. Moreover, infants of mothers with diabetes showed poorer and immature sucking patterns contributing to the difficulties to breastfeed for those mothers in the first days postpartum (199). Protective factors associated with both higher rates of intention to breastfeed and exclusive breastfeeding included attending antenatal classes and having antenatal care delivered by a health-care provider other than an obstetrician. Indeed, women who received antenatal care from a family physician or other health-care providers were respectively 2 and 3 times more likely to exclusively breastfeed (184). Patient education with prenatal information and postnatal counselling on breastfeeding have been shown to lead to similar breastfeeding rates in women with type 1 diabetes as the population without diabetes (181).

Use of noninsulin antihyperglycemic agents during breastfeeding. Few studies have examined breastfeeding and the use of noninsulin antihyperglycemic agents. Three case series found metformin in the milk and plasma of breastfeeding women who were taking metformin 500 mg 2 or 3 times daily, but infant exposure was well below the 10% "level of concern" (0.182% to 0.65%) (200–202). A study looking at weight, height and motor-social development up to 6 months of age in children of mothers taking metformin while breastfeeding showed normal development and no difference from formula-fed infants (203). One case series that studied women taking glyburide or glipizide while breastfeeding found neither drug in the breastmilk, and the maximum theoretical infant dose was well below 10% (<1.5%), with no hypoglycemia found in the 3 infants tested (204). Although metformin and glyburide can be considered for use during breastfeeding, further long-term studies are needed to better clarify the safety of these drugs. Finally, there are no human studies to date looking at thiazolidinedione (TZD), glucagon-like polypeptide-1 (GLP-1) receptor agonist, dipeptidyl peptidase-4 (DPP-4) inhibitor or sodium-glucose cotransporter-2 (SGLT2) inhibitor use while breastfeeding and, therefore, they should not be taken during breastfeeding.

Use of insulin and newer insulin analogues during breastfeeding. There is no contraindication for women with diabetes treated with insulin to breastfeed (175). Exogenous insulins are excreted into breastmilk, including newer insulin analogues (i.e. aspart, detemir, glargine, glulisine, lispro). Insulin is a normal component of breastmilk (205,206) and similar levels were found in the milk of women with type 1 diabetes, type 2 diabetes and women without diabetes, suggesting an active transport of endogenous and exogenous insulin into breastmilk (207). Insulin normally found in breastmilk of mothers with or without diabetes is thought to be required for intestinal maturation of the infant and could act as a positive modulator of the immune response to insulin as suggested by certain groups (208–210).

Benefits of breastfeeding. Breastfeeding immediately postpartum can be part of an early feeding strategy to reduce the risk of neonatal hypoglycemia in women with diabetes (211). Breastfeeding for more than 4 months has also been shown to be protective against the development of diabetes (OR 0.29, 95% CI 0.13–0.63) at 21 years of age in a cohort of 3,595 young adults (212). It was previously thought that early introduction of cow's milk protein could be involved in the development of beta cell autoimmunity in infants at risk for type 1 diabetes. However, a randomized trial comparing the use of a hydrolyzed formula with smaller foreign proteins, compared with a conventional formula containing cow's milk protein, did not reduce the incidence of diabetes-associated autoantibodies 7 years after exposure in offspring with genetic susceptibility to type 1 diabetes and a family member with type 1 diabetes. These data do not support a short-term benefit from the use of hydrolyzed formula but a longer effect on disease prevalence is under study (213) (see Reducing the Risk of Developing Diabetes chapter, p. S20). Finally, along with other known benefits of breastfeeding for mother and

child, although not specific to women with pre-existing diabetes, there is evidence that breastfeeding is a significant protective factor against obesity in children (214–216).

In summary, women with pre-existing diabetes should be encouraged to breastfeed immediately after delivery and for at least 4 months postpartum, as it may contribute to the reduction of neonatal hypoglycemia, offspring obesity and prevent the development of diabetes. Furthermore, exclusive breastfeeding up to 6 months and continuation of breastfeeding up to 2 years with appropriate complementary feeding has shown further benefits and is currently recommended for all women by the Canadian Paediatric Society (217,218). Health-care providers should pay particular attention to promoting breastfeeding in women with diabetes (184,189), especially in the context of maternal obesity, since this high-risk population has the lowest rates of breastfeeding despite demonstrated benefits for mother and child. Attention should be paid, however, to potential increased risk of hypoglycemia, especially during night feeding, in breastfeeding women with type 1 diabetes.

Postpartum contraception

Effective contraception is an important consideration until proper preparation occurs for a subsequent pregnancy in women with pre-existing diabetes. Regarding the choice of a contraceptive method, the same motivations and restrictions apply to women with type 1 and type 2 diabetes as with other women. Evaluation includes discussing women's preferences for a contraceptive method that will ensure compliance. Absolute and relative contraindications to estrogen (breastfeeding, high BP, and microvascular and CV diabetes-related complications) or to an intrauterine device (IUD) (219) also apply. The progesterone-only contraceptive and IUD are safe with breastfeeding (220).

GDM

Prevention and risk factors

The incidence of GDM is increasing worldwide. The global prevalence of hyperglycemia during pregnancy has been estimated at 16.9% (21.4 million live births in 2013) using the World Health Organization criteria (221). A higher proportion of women entering pregnancy at an older age and/or with obesity contribute to this increase in prevalence, along with changes in screening strategies and diagnostic criteria. There is a need for an effective and acceptable intervention that will prevent the development of GDM. Such an approach has the potential to improve maternal and child health, with significant savings to the health-care system.

Understanding the pathophysiology of GDM and its risk factors is important for the development of preventive strategies. The GDM population includes a heterogeneous group of women with different metabolic profiles when exposed to pregnancy hormones. Various presentations include:

- Hyperglycemia that likely preceded the pregnancy (e.g. impaired glucose tolerance (IGT), elevated first trimester fasting glucose, overt diabetes in pregnancy, monogenic diabetes)
- Reduced and/or falling insulin secretory capacity (e.g. developing type 1 diabetes)
- Significant insulin resistance from early pregnancy (e.g. polycystic ovary syndrome, women with overweight or obesity, some specific ethnic groups)
- A combination of factors (e.g. family history of diabetes, previous GDM, genetic predisposition for GDM/type 2 diabetes (222,223)).

As insulin sensitivity decreases substantially with pregnancy (224), not all cases of GDM can be prevented. Studies need to focus on identifying the potential groups of women who can benefit from preventive interventions and adapt such strategies to their condition (e.g. preconception vs. during pregnancy, women with obesity or leanness). Considering the heterogeneity of GDM, it seems obvious that tailored recommendations will emerge for each identified group of at-risk women.

More than 30 randomized controlled trials on GDM prevention have been reported. The interventions tested to date include different diets sometimes combined with diverse physical activity plans, vitamin D supplements, myo-inositol, probiotics and metformin. However, only 3 interventions have demonstrated a significant risk reduction for GDM to date. Effective measures included healthy eating, myo-inositol supplementation and probiotic treatment. Among evaluated interventions, diet-based interventions appear to show the most potential for preventing GDM, especially when directed toward women with overweight or obesity as demonstrated in 3 meta-analyses (225–227). The first meta-analysis (225) of 14 randomized controlled trials (n=2,422 pregnant women) compared interventions with standard care in women with risk factors for GDM represented essentially in all studies by maternal overweight and obesity. Interventions evaluated and compared to standard care included diet, physical activity alone, lifestyle changes (diet and physical activity) and metformin. Dietary interventions were associated with a statistically significant lower incidence of GDM (OR 0.33; 95% CI 0.14-0.76) and gestational hypertension (OR 0.28; 95% CI 0.09–0.86) compared to standard care. There was no statistically significant difference in the incidence of GDM or in the secondary outcomes with physical activity alone, lifestyle changes (diet and physical activity) or metformin use compared to standard care. In the 3 randomized controlled trials focusing on diet, a total of 455 women were included, with comparable mean maternal age and mean BMI (36.1 vs. 36.4 kg/m^2) in controls. GDM prevalence decreased from 18% to 7% in the diet groups. Healthy eating intervention consisted of a consultation with a trained dietitian, weighing at each antenatal visit and review of food records, but the duration and number of sessions differed among studies. In the second meta-analysis (226), there was a trend toward a reduced risk of GDM in diet-based intervention groups, but a significant reduction in GDM was noted again in subgroup analysis of pregnant women with obesity or overweight (RR 0.40, 95% CI 0.18–0.86). Finally, the composition of protein content of daily meals may be important as a large prospective cohort study demonstrated that an increased prepregnancy intake of animal protein, in particular red meat, was significantly and positively associated with GDM risk, while vegetable protein intake, specifically nuts, was significantly and inversely associated with GDM risk (228).

Mixed-approach interventions, including diet, physical activity and lifestyle modifications, do not appear to prevent GDM in some studies (225,226,229) but seem effective in a recent meta-analysis when introduced before 15 weeks of gestation (227); methodological problems with this study involving the inclusion of studies of diet alone and physical activity alone make this conclusion less reliable and in need of confirmation by further analyses. It can be argued that the complexity of healthy behaviour interventions, the variability of adherence and delay before introduction, as well as the heterogeneity of the maternal metabolic profile and diagnostic criteria in GDM are the main factors that may explain the discrepancies seen and inconclusive evidence for healthy behaviour interventions. Finally, results of meta-analyses on interventions based solely on physical activity programs to prevent GDM are not impressive (small protective effect [230] vs. nonsignificant impact [225]) and studies seem often underpowered with suspected low protocol adherence.

Studies looking at metformin use for GDM reduction in women with obesity (231) and with PCOS (232) have not shown benefit. Moreover, studies are currently insufficient to support clear clinical recommendations regarding vitamin D supplementation in pregnancy to prevent GDM. Only 3 of 8 observational studies (233) and 1 meta-analysis (234) demonstrate a significant inverse relationship between risk of GDM and maternal vitamin D status. Also, incidence of GDM and other obstetrical outcomes were not influenced by vitamin D supplementation (235). Overall, there is currently limited evidence to support lifestyle, physical activity interventions, metformin or vitamin D supplements for GDM prevention.

Probiotics combined with diet and myo-inositol have shown benefit for GDM prevention (226), but these nutritional supplements were assessed in only 1 trial each. One randomized controlled trial demonstrated a 60% GDM reduction with the use of antenatal probiotics, with no impact on GWG (236,237). Moreover, probiotics did not show an impact on glycemic control in GDM women, but attenuated the normal pregnancy-related rise in low-density lipoprotein cholesterol (LDL-C) levels in the third trimester (238). Similar results were obtained with myo-inositol supplements with a 58% risk reduction of developing GDM in pregnant women with overweight or obesity (239,240). However, those studies have been conducted by only 1 research group, with small sample sizes and these results have not been replicated. Before any further recommendations are made for probiotics or myo-inositol supplements for GDM prevention, large randomized trials are needed.

Finally, a recent meta-analysis demonstrated that excessive GWG, occurring in the first and second trimester, increased the risk of GDM by a factor of 1.4, with similar effect in women with normal weight, overweight or obesity (241). Also, BMI increase observed in the inter-pregnancy period in women with normal BMI or with a BMI >27 kg/m^2 is associated with higher risk of GDM in their second pregnancy (242). On the other hand, a decrease in inter-pregnancy BMI in women with overweight or obesity significantly decreases their risk of developing GDM in their second pregnancy, reinforcing the importance of a healthy diet and lifestyle during the preconception period for women with overweight or obesity (242). Along these lines, bariatric surgery is becoming increasingly common for the treatment of obesity, and studies looking at pregnancy outcomes following bariatric surgery have found both benefits (decreased GDM, hypertensive disorders, LGA infants) but also some adverse outcomes (SGA infants, preterm deliveries and NICU admissions) (243). As suggested by most experts and the British Obesity and Metabolic Surgery Society (244,245), women should delay pregnancy at least 12 to 18 months after bariatric surgery to limit adverse pregnancy outcomes and allow weight stabilization and replenishing of all vitamins and microelement deficiencies before conception. A study on children born before and after maternal surgical weight loss demonstrated reduced obesity rate and improved cardiometabolic profiles during childhood and adolescence in offspring born after maternal bariatric surgery, positioning bariatric surgery as 1 of the potential options to limit intergenerational transmission of obesity (246).

In summary, evidence is limited but current literature suggests that the only effective GDM preventive measure in early pregnancy that can be considered in high-risk women, especially prepregnant women with obesity, is a healthy diet and close follow up of weight gain to prevent excessive GWG. Nutritional supplements, such as probiotics and myo-inositol, have shown some encouraging results, but these need to be replicated in larger randomized trials. More studies using the same set of diagnostic criteria are needed and focus should be put on specific populations (prepregnant women with obesity, prior GDM and/or PCOS, as well as women with excessive GWG) to be able to develop effective preventive interventions tailored for those high-risk populations to reduce GDM prevalence.

Screening and diagnosis of GDM

Early screening. Screening for diabetes in the first trimester should be considered for diagnosing overt diabetes (diabetes present before pregnancy) in women who are at risk (see Screening for Diabetes chapter, p. S16), including those with a history of previous GDM. The ability to predict abnormal results on glucose screening tests at 24 to 28 weeks and risk of continued dysglycemia postpartum are other, but less compelling, reasons cited to screen in the first trimester.

The test of choice for early screening should be based primarily on the ability to predict poor obstetrical outcomes, which may be modifiable by lifestyle or pharmacological intervention. There are 2 strategies for testing glucose levels in early pregnancy—using the nonpregnancy-recommended screening tests (FPG or A1C) or using the typical 24- to 28-week gestational diabetes screening (50 g glucose challenge test [GCT] and/or 75 g oral glucose tolerance test [OGTT]) criteria (see below). To apply nonpregnant FPG or A1C criteria in early pregnancy does not take into account that both decrease early in pregnancy and may lead to underdiagnosis in women with pre-existing diabetes. On the other hand, there has been no rigorous validation that criteria accepted for the diagnosis of GDM in the second or third trimester are appropriate for use in the first trimester.

First trimester FPG levels are associated with macrosomia and increased caesarean section rates, as well as an increased risk of second-trimester diagnosis of GDM. The results of a retrospective cohort study (n=6,129) suggest that this association between first trimester fasting glucose and later diagnosis of GDM, macrosomia and caesarean section risk is a graded relationship with no clear cut point (247). In another large cohort study (n=17,186 pregnancies), 39% of women with a first trimester FPG over the GDM diagnostic criteria (5.1 mmol/L), will no longer have an elevated FPG if rescreened at 24 to 28 weeks (248). This suggests that first trimester FPG is not reliable for predicting second-trimester GDM.

First-trimester A1C has been used to predict risk of poor obstetrical outcomes, later development of GDM and persistence of postpartum dysglycemia. In 1 study of 16,122 women screened at a median of 47 days gestation, there were higher rates of major congenital anomalies (RR 2.67, 95% Cl 1.28–5.53), preeclampsia (RR 2.42, 95% Cl 1.28–5.53), shoulder dystocia (RR 2.47, 95% CI 1.05–5.85) and perinatal death (RR 3.96,95% Cl 1.54–10.16) with an A1C of 5.9% to 6.4% in the first trimester (249). However, only 23% of women in that study returned for a first-trimester OGTT, highlighting the low uptake of the OGTT in the first trimester. A retrospective cohort study of 2,812 women compared first trimester A1C to 24-week OGTT and found that an A1C of 5.7% to 6.4% had a 13% sensitivity and 94% specificity for predicting GDM based on a second-trimester 75 g OGTT (250). Another recent study in a multiethnic population of 1,156 women who underwent first trimester A1C and 24- to 28-week 2-stage glucose tolerance test, 48 out of 1,180 had an A1C of 5.9% to 6.4%, which was associated with a 3-fold higher rate of preeclampsia (OR 3.539, 95% CI 1.086–11.532) and macrosomia (OR 3.1, 95% CI 1.127–8.603). However, an elevated first trimester A1C shows a low sensitivity (14.5%) but high specificity (97.5%) for predicting second-trimester GDM (251). In a small cohort study of 160 women, the best cut-off for first trimester A1C to differentiate a diagnosis of postpartum type 2 diabetes was ≥5.9% (252). Thus, a first trimester A1C ≥5.9% appears to confer risk of adverse obstetrical outcome, later diagnosis of GDM and postpartum diabetes. Combining a first trimester FPG of 5.1 to 7.0 mmol/L or A1C 5.7% to 6.4%, is more predictive of need for medical management than when GDM is diagnosed later in pregnancy (253).

Although consideration can be given to treatment of women with A1C 5.9% to 6.4% in the first trimester given the evidence of adverse pregnancy outcomes, whether intervention earlier in pregnancy makes a difference remains unknown. In 1 small cohort study, early intervention appeared to lower the risk of preeclampsia (249). A larger cohort trial using a 75 g OGTT for screening high-risk women earlier in pregnancy continued to show higher rates of hypertensive disorders, preterm delivery, caesarean section rates, macrosomia, and neonatal intensive care despite intervention (254). Although widely used before 24 weeks of gestation for assessment of risk in women at high risk of developing GDM, the 75 g OGTT has no validated thresholds for diagnosis of GDM at this gestational age and there is no evidence yet to support a benefit for earlier management in those that screen positive by whatever threshold is used. If an OGTT is performed before 24 weeks of gestation and is negative by the thresholds used to diagnose GDM after 24 weeks, this test needs to be repeated between 24 to 28 weeks.

Finally, all women with diabetes diagnosed during pregnancy, whether diagnosed in the first trimester or later in pregnancy, should be retested postpartum. In 1 study, in women 6 to 8 weeks postpartum who had an A1C ≥6.5% or FPG ≥7.0 at 24 to 28 weeks during pregnancy, 21% had continued diabetes, 37% had impaired fasting glucose (IFG) or IGT and 41% had normal glucose levels (248,250,255).

Screening and diagnosis

As previously outlined in the *Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* (CPG), Diabetes Canada continues to support universal screening and diagnosis of GDM based on large randomized control trials and meta-analyses demonstrating that treatment of women with GDM reduces fetal overgrowth, shoulder dystocia and preeclampsia (85,256–259). Justification for supporting universal screening for GDM is outlined in detail in the 2013 CPG (260). Assuming universal screening, the method of screening can be either a sequential 2-step or a 1-step process. Methods for sequential screening include the use of glycosuria, A1C, FPG, random plasma glucose (RPG) and a glucose load. Aside from the glucose load, all the other methods mentioned have not been adopted due to their poorer performance as screening tests in most populations (261–267). The most common glucose test used in sequential screening is the 50 g GCT performed between 24 to 28 weeks of gestation, and it is the screening test recommended by Diabetes Canada in the 2013 and 2018 guidelines. The performance of the GCT as a screening test depends on the cut-off values used, the criteria for diagnosis of GDM and the prevalence of GDM in the screened population. As previously discussed in the 2013 CPG, despite its limitations, the 50 g GCT is practical, accepted by pregnant women and caregivers and retains a >98% negative predictive value for GDM in most populations (268). Results from a Canadian prospective study show that sequential screening is associated with lower direct and indirect costs while maintaining equivalent diagnostic power when compared with 1-step testing. Recent observational data demonstrated the feasibility and good uptake of the 2-step approach (269).

An additional question is whether there is a GCT threshold above which GDM can be reliably diagnosed without continuing to the diagnostic OGTT. It is recognized that using a cut-off of ≥11.1 mmol/L after a 50 g GCT will result in a small number of women receiving an erroneous diagnosis of GDM (270). However, these women are at increased risk of adverse perinatal outcomes and might benefit from the same management as those diagnosed with GDM (271), especially since those with a glucose screen >11.1 mmol/L were found to have a 3.7-fold increased rate of insulin treatment compared to women diagnosed as GDM by National Diabetes Data Group (NDDG) or Carpenter and Coustan criteria (272). We thus have decided to maintain the recommendation from the 2013 CPG to diagnose GDM if the glucose level 1 hour after the 50 g GCT is ≥11.1 mmol/L.

What is the optimal method of diagnosis?

Since there is no clear glucose threshold above which pregnancy outcomes responsive to glycemic management occur (268,273,274), controversy persists as to the best diagnostic thresholds to define GDM. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel decided to create new diagnostic thresholds for GDM based on data from the Hyperglycemia and Adverse pregnancy Outcome (HAPO) study. IADPSG thresholds are the maternal glucose values from HAPO associated with a 1.75-fold increase of LGA, elevated C-peptide, high neonatal body fat or a combination of these factors, compared with the mean maternal BG values of women studied in HAPO. These arbitrary thresholds, when applied to the HAPO cohort, led to a GDM incidence of 17.8%. The National Institute of Health (NIH) 2013 Consensus Conference summary statement stated that "at present, the panel believes that there is not sufficient evidence to adopt a 1-step approach, such as that proposed by the IADPSG" (275). However, since this publication, national organizations have published guidelines that are divergent in their approach to screening and diagnosis of GDM (276–280), thus perpetuating the international lack of consensus on the criteria for diagnosis of GDM.

Given the lack of agreement that persists in the international community, the 2013 Canadian Diabetes Association Expert Committee acknowledged the controversy and opted to continue to recommend the "preferred" sequential 2-step approach (Figure 1) while recognizing the option of the 1-step IADPSG approach as an "alternative" strategy (Figure 2) (260). The "preferred" approach for sequential screening consists of a 50 g GCT followed by a 75 g OGTT using the glucose thresholds that result in an (also arbitrary) OR of 2.0 for the increased risk of LGA and cord C-peptide (fasting ≥5.3 mmol/L, 1 hour ≥10.6 mmol/L, 2 hours ≥9.0 mmol/L) (273) (Table 2). However, it was recognized that the IADPSG 1-step strategy has the potential to identify a subset of women who would not otherwise be identified as having GDM and could potentially benefit with regards to certain perinatal outcomes. Therefore, a diagnostic strategy consistent with the IADPSG approach of a 1-step 75 g OGTT using the glucose thresholds that result in an OR of 1.75 for the risk of LGA and cord C-peptide was added as an "alternative" method (Figure 2). As outlined in the 2013 CPG, those who believe that all cases of hyperglycemia in pregnancy need to be diagnosed and treated (i.e. increased sensitivity over specificity) will support the use of the 1-step method of GDM diagnosis.

Some data to support Diabetes Canada's "preferred" strategy can be found in an analysis of 1,892 women with mild untreated glucose intolerance (281). In this study, perinatal outcomes for women with 75 g OGTT results that were positive by HAPO 1.75 OR thresholds (Diabetes Canada alternative) were compared to women with 75 g OGTT results that were positive by HAPO 2.0 OR thresholds (Diabetes Canada preferred). LGA rate and birth weight progressively increased with more dysglycemia and were increased in both groups. However, in this study, only women who were positive by HAPO 2.0 OR thresholds had an increased incidence of preeclampsia, preterm delivery, primary caesarean delivery, shoulder dystocia, ponderal index, transient tachypnea and neonatal hypoglycemia after adjustment for confounders (281).

Impact of adoption of IADPSG criteria

Since the publication of the IADPSG consensus thresholds, there have been numerous retrospective studies that have examined the impact of adoption of these criteria. It is difficult to apply the results

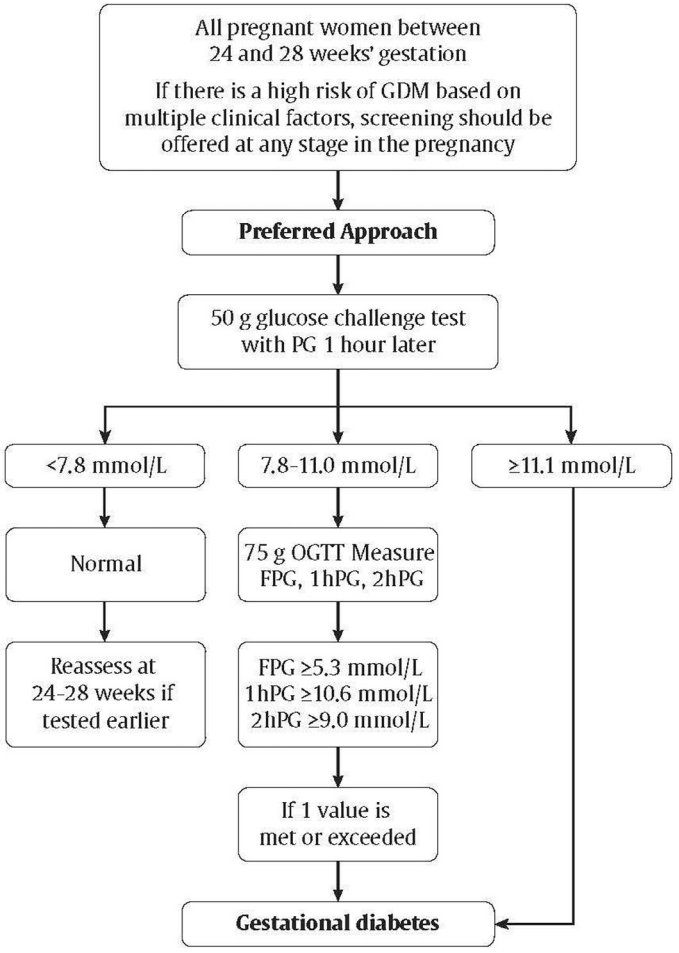

Figure 1. Preferred approach for the screening and diagnosis of gestational diabetes.
1hPG, 1-hour plasma glucose; *2hPG*, 2-hour plasma glucose; *FPG*, fasting plasma glucose; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test; *PG*, plasma glucose.

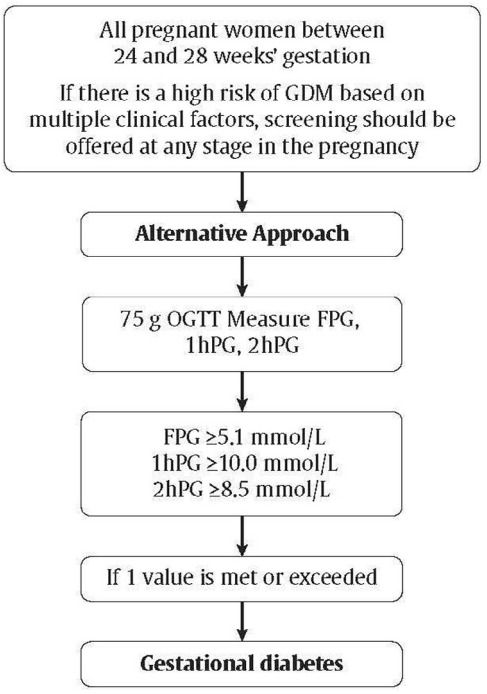

Figure 2. Alternative approach for the screening and diagnosis of gestational diabetes.
1hPG, 1-hour plasma glucose; *2hPG*, 2-hour plasma glucose; *FPG*, fasting plasma glucose; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test; *PG*, plasma glucose.

Table 2
Differences between selecting an OR of 1.75 vs. 2.0 for the primary outcome in the HAPO cohort (273,479)

	OR 1.75	OR 2.0
Threshold glucose levels (mmol/L)		
Fasting	5.1	5.3
1 hour	10.0	10.6
2 hour	8.5	9.0
% of HAPO cohort that met ≥1 glucose threshold	16.1%	8.8%

HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; OR, odds ratio.

of these studies to clinical practice due to their retrospective nature and the wide variation in the comparison groups used. In all of these studies, adoption of IADPSG criteria has led to an increase in the number of cases diagnosed while the impact on perinatal outcomes is inconsistent (282–287). Studies comparing pregnancy outcomes before and after changing from a variety of different GDM diagnostic criteria to the IADPSG criteria show differing results. LGA (285) was lower in 1 study and caesarean delivery was lower in several studies (282,285) after adoption of the IADPSG criteria. However, others did not find reductions in LGA (282,283,286,287), and 1 study found an increase in primary caesarean section rate (286).

Given this lack of evidence, it is possible that the decision regarding the recommended screening method will be determined by the economic implications on health-care resources. Decision analysis modelling studies done in other countries (285,288–290) have yielded a variety of results and many are of questionable applicability in the Canadian setting because of differing cost and screening and diagnostic strategies.

A small observational study from Ireland suggested that maternal BMI may be an important consideration in choice of which diagnostic thresholds to use (291). When this group used the IADPSG diagnostic thresholds for all women, they observed a beneficial effect of GDM treatment in women with obesity, but not in women with BMI <25 kg/m^2. Furthermore, secondary analysis of the Landon et al trial, that used a 2-step screening approach, found that GDM therapy had a beneficial effect on fetal growth only in women with class 1 and 2 obesity and not in women with normal weight or with more severe obesity (292).

In summary, until more high-quality information comparing the 2013 CPG "preferred" and "alternative" approaches for GDM screening and diagnosis becomes available, the committee agreed it was best to maintain the same diagnostic criteria as those introduced by the 2013 CPG. Further higher-quality evidence would be helpful in establishing if maternal BMI and other clinical risk factors should guide which diagnostic thresholds are used. Most cost analysis evaluations support a sequential screening approach to GDM. The 2018 Diabetes Canada Expert Committee recognizes the drawbacks of having different diagnostic strategies and different thresholds for the same 75 g OGTT but at this time there is insufficient evidence to support 1 strategy over the other (293). Therefore, adequately powered prospective studies to compare these 2 approaches are needed.

Monogenic diabetes in pregnancy

Since pregnancy may be the first time in their lives that women undergo glucose screening, monogenic diabetes may be picked up for the first time in pregnancy. Monogenic diabetes first diagnosed

in pregnancy should be suspected in the women with GDM who lack risk factors for GDM and type 1 diabetes and have no autoantibodies (see Definition, Classification, and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10). A detailed family history can be very helpful in determining the likely type of monogenic diabetes. This is important because the type of monogenic diabetes influences fetal risks and management considerations. The most common forms of monogenic diabetes in Canada are maturity onset diabetes of the young (MODY) 2 (heterozygotes for glucokinase [GCK] mutations) or MODY 3 (hepatocyte nuclear factor [HNF] 1 alpha mutation) (294). A history of family members with longstanding isolated elevated FBG with mild A1C elevations that do not progress to "frank" diabetes over a long duration is suggestive of MODY 2. During pregnancy, the usual phenotype for MODY 2 of isolated elevated FBG is not always seen, even though this phenotype may be present outside of pregnancy in the same woman (295). Fetal carriers of GCK mutations (50% of fetuses of an affected parent) do not usually have macrosomia. Fetuses without the GCK mutation of mothers with GCK mutation are at increased risk of macrosomia. The best way to manage women with GCK mutation during pregnancy has yet to be established, but regular fetal growth assessment can aid in the establishment of appropriate glucose targets during pregnancy for women with documented or strongly suspected GCK mutations.

A family history where approximately 50% of family members over 3 generations have diabetes, especially if they are thin and known to be very responsive to insulin secretagogues is highly suggestive of MODY 3 (HNF1 alpha) mutation. MODY 1 (HNF4 alpha mutation) has a similar phenotype to MODY 3 but is much less common. These forms of monogenetic diabetes have greater increased risk of macrosomia and neonatal hypoglycemia that may be prolonged especially in neonates that have MODY 1 (HNF4 alpha mutation). Although women with these later forms of monogenic diabetes are usually exquisitely sensitive to sulfonylureas, they should be transitioned to insulin as they prepare for pregnancy or switched to insulin during pregnancy, if this has not occurred preconception, for the same reasons as avoiding glyburide use in women with GDM.

Management: Healthy behaviour interventions

Weight gain. The 2009 IOM guidelines for weight gain during pregnancy were developed for a healthy population and little is known regarding optimal weight gain in women with GDM. Retrospective cohort studies of GDM pregnancies show that only 31.7% (296) to 42% (297) had GWG within IOM guidelines. Those gaining more than the IOM recommendations had an increased risk of preeclampsia (297), caesarean deliveries (296,297), macrosomia (296,297), LGA (296–298) and GDM requiring pharmacological agents (297). Modification of IOM criteria, including more restrictive targets of weight gain, did not improve perinatal outcomes of interest (296). A large population-based study including women with GDM, concluded that while pre-pregnancy BMI, GDM and excessive GWG are all associated with LGA, preventing excessive GWG has the greatest potential of reducing LGA risk (299). These researchers suggest that, in contrast to obesity and GDM prevention, preventing excessive GWG may be a more viable option as women are closely followed in pregnancy.

A large number of women with overweight or obesity and with GDM gain excessive weight in pregnancy (296,298) and a large proportion exceed their IOM total target by the time of GDM diagnosis (296). A systematic review found that pregnant women with overweight or obesity who gain below the IOM recommendation, but have an appropriately growing fetus, do not have an increased risk of having a SGA infant (118), leading some to recommend that encouraging increased weight gain to conform with IOM guidelines will not improve maternal or fetal outcomes (300). However, other researchers urge caution as they have found that, in women with overweight or obesity and GDM, a weight loss or gain of ≤5 kg was associated with SGA and decreases in neonatal fat mass and lean body mass, including length and head circumference (301). The findings of a retrospective cohort study including women with overweight or obesity and with GDM show that after adjusting for confounding variables, modest weight loss after GDM diagnosis may not adversely impact fetal growth among those in obesity class II/III and those exceeding the IOM guidelines for total GWG at the time of GDM diagnosis (302).

A Cochrane review (49 trials of 11,444 women) was performed to evaluate the effectiveness of diet or exercise or both in preventing excessive gestational weight gain and associated adverse pregnancy outcomes (303). Study interventions involved mainly diet only, exercise only and combined diet and exercise interventions compared with standard care. Results show that diet or exercise or both reduced GWG on average by 20%. Low glycemic load (GL) diets, supervised or unsupervised exercise only or diet and exercise in combination all led to similar reductions in the number of women gaining excessive weight in pregnancy. There was no clear difference between intervention and control groups with regards to pre-eclampsia, caesarean section, preterm birth and macrosomia. In subgroup analysis by risk, high-risk women (having overweight or obesity, or with or at risk of GDM) who received combined diet and physical activity intervention experienced a 15% reduction in macrosomia.

Further studies are needed to develop weight gain guidelines for GDM patients and to determine whether weight gain less than the IOM guidelines or weight loss in pregnancy is safe. Until this data are available, women with GDM should be encouraged to gain weight as per the IOM guidelines for the BMI category to reduce adverse maternal and neonatal outcomes and postpartum weight retention.

Nutrition therapy. Nutrition therapy is a cornerstone for managing GDM. All women at risk for or diagnosed with GDM should be assessed, counselled and followed up by a registered dietitian when possible (304–306). Nutrition therapy should be designed to promote adequate nutritional intake without ketosis, achievement of glycemic goals, appropriate fetal growth and maternal weight gain (307–310). Recommendations for nutrition best practice (304) and a review of the role of nutrition therapy in GDM management (311) is available.

A great variety of diets are used for managing GDM. While carbohydrate moderation is usually recommended as first-line strategy to achieve euglycemia (312), evidence available to support the use of a low-glycemic-index (GI) diet is increasing. A randomized controlled trial of 70 healthy pregnant women, randomized to low glycemic index (GI) vs. a conventional high-fibre diet from 12 to 16 weeks' gestation, showed a lower prevalence of LGA without an increase in SGA in the low-GI group (313). This led to the hypothesis that a low-GI diet may be beneficial in women with GDM. An earlier systematic review of 9 randomized controlled trials, in which 11 different diet types were assessed within 6 different diet comparisons, did not support the recommendation of 1 diet type over another as no significant differences were noted in macrosomia, LGA or caesarean section rates (314). However, a more recent systematic review and meta-analysis does support the use of low GI diets (315). In this review and meta-analysis of 9 randomized controlled trials (n=884 women with GDM), 3 meta-analyses were performed according to type of dietary intervention used—low-GI, total energy restriction and low-carbohydrate diet. Only the low-GI diet was associated with less frequent insulin use and lower newborn weight without an increase in numbers of SGA and macrosomia (315). Results of a meta-analysis of 5 randomized controlled trials (316) and a systematic review (317) in GDM patients showed that

low-GI diets reduce the risk of macrosomia and LGA, respectively. Low-GI diets are associated with lower postprandial blood glucoses in recent randomized controlled trials (318,319).

In summary, current evidence although limited, suggests that women with GDM may benefit from following a low-GI meal pattern (320). Thus, advice on meal planning for women with GDM should emphasize a healthy diet during pregnancy, with a minimum of 175 g/day of carbohydrate (321) distributed over 3 moderate-sized meals and 2 or more snacks (1 of which should be at bedtime), (304,311) as well as replacing high-GI foods with low-GI ones.

Physical activity. In combination with nutritional intervention, physical activity appears to be more effective for GDM management than GDM prevention. A recent review reported that 5 of 7 studies (71%, 5 randomized controlled trials, 1 case-control, 1 self-enrolment) demonstrated a positive impact of physical activity interventions on GDM management by reducing insulin use and/or by improving glycemic control in women with GDM (322). Adherence to the physical activity program was good overall except among the 2 studies that were unsuccessful at improving glycemic control; 1 reported low compliance with physical activity recommendations, and the other proposed an exercise program with a higher level of intensity (>70% of maximal heart rate). No studies had an effect on infant birth weight or macrosomia rate and only 1 was successful in reducing GWG. It can be argued that these studies were not powered enough to demonstrate any impact on birthweight or on adverse pregnancy outcomes. Indeed, relevant limitations for these studies include the following: samples were small (mean of 43 participants per study), participants had different metabolic profiles and risks factors, and different diagnostic criteria for GDM were used.

The best type of intervention that should be recommended is unclear since all the successful programs used different exercise modalities in terms of intensity, type, duration and frequency. More recently, an initiative in India, the Wings Project, demonstrated that an intervention based on increasing total footsteps with pedometers was able to improve glycemic control in 151 women with GDM and reduce adverse neonatal outcomes in the more active tertiles when compared to their GDM counterparts in the upper tertiles of sedentary behaviour (323). Since no exercise-related injuries were experienced during pregnancy in all those studies, physical activity intervention seems safe to recommend.

All together, current knowledge suggests that physical activity interventions in women with GDM should be encouraged unless obstetrical contraindications exist as physical activity may be an important component of GDM management. However, identification of a specific program of physical activity that should be prescribed to GDM women is currently not possible. Further studies are needed involving larger populations to enable the prescription of an evidence-based physical activity intervention.

Glycemic control. In a systematic review of reports of BG levels in non-GDM pregnancies, normal BG levels during later pregnancy (mean and 1 SD above mean) were: fasting 3.9±0.4 mmol/L, 1 hour postprandial 6.1±0.7 mmol/L and 2 hours postprandial 5.5±0.6 mmol/L with a mean BG of 4.9±0.6 mmol/L (84). The peak postprandial BG occurred at 69±24 minutes (84). However, it should be noted that the mean FBG derived from the total of 255 subjects in this report was 0.6 mmol/L lower than that reported in the HAPO study (273). The HAPO study was the largest prospective study of glycemia in pregnancy and reported a mean FBG of 4.5±0.4 mmol/L, derived from 23,316 pregnant women (273). BG levels in pregnant women with obesity without diabetes were slightly higher than their lean counterparts in a study in which CGM was performed in early and late pregnancy after placing pregnant women with obesity or normal weight on a controlled diet (324).

Importantly, it has been demonstrated that the diagnostic OGTT values were not the best predictors of outcomes whereas CBG levels during treatment were strongly correlated to adverse pregnancy outcomes (325). For women with GDM, good outcomes have been reported using targets of FBG <5.3 mmol/L, 1 hour postprandial BG <7.8 mmol/L and 2 hours postprandial <6.7 mmol/L (86–89) and are close to the targets of the 2 randomized controlled trials showing benefit for the treatment of GDM (85,256). Even if BG can normally and physiologically decrease during pregnancy below the traditional level of 4.0 mmol/L, women receiving insulin should maintain BG >3.7 mmol/L to avoid repeated hypoglycemia—see *Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy: Definition of hypoglycemia during pregnancy*, for further details. On the other hand, recent studies have questioned the upper limit of the FBG target. A systematic review of 34 studies (9,433 women) suggests that a FBG ≤5.0 mmol/L was associated with a protective effect on the development of macrosomia (OR=0.53, 95% CI 0.31–0.90, p=0.02), LGA (OR=0.68, 95% CI 0.53–0.88, p=0.01), neonatal hypoglycemia (OR 0.65, 95% CI 0.49–0.85, p=0.01), hyperbilirubinemia (OR 0.63, 95% CI 0.43–0.90, p=0.01) and preeclampsia (OR 0.47, 95% CI 0.31–0.72, p=0.01) when it was evaluated for the third trimester (326). Risks of maternal hypoglycemia or fetal low birth weight were not evaluated in this review and adjustment for maternal BMI and different diagnostic criteria for GDM was not performed. However, this meta-analysis supports the work of Rowan et al demonstrating that the lowest risk of complications was seen when fasting CBG was <4.9 mmol/L (mean SD 4.6±0.3 mmol/L) (325). Even if the frequency of SGA infants was lower across the tertile of mean maternal fasting glycemia in this study, SGA rate in women with the lowest mean FBG was not increased and was, in fact, comparable with the rate of the background population. SGA rate was inversely correlated with maternal weight gain before assessment, suggesting that SGA could be partly prevented by adequate follow up of GWG in those women.

Overall, data suggests that a reduced FBG target of ≤5.0 mmol/L for GDM women would limit LGA and other perinatal complications rates. However, large, well-conducted and randomized controlled trials comparing different BG targets are needed to directly address optimal fasting and postprandial BG targets. Further studies should also assess the risk of maternal hypoglycemia, SGA, insulin use and cost-effectiveness of such modification.

Adjustment of glycemic targets based upon fetal abdominal circumference on third-trimester ultrasound

Despite reduced perinatal morbidity with interventions to achieve euglycemia in women with GDM, increased prevalence of macrosomia persists in this population. To improve outcomes, 4 randomized controlled trials (327–329) have examined the use of fetal abdominal circumference (AC) as measured sonographically and regularly in the third trimester to guide medical management of GDM. This approach involves using stricter maternal BG targets (FBG <4.5 and 2-hour postprandial BG <5.6 to 6.1 mmol/L), and an increased use of insulin, if needed, when the fetal AC measures ≥75th percentile (327–329) or ≥70th percentile (330) and conversely relaxed glycemic objectives (FPG <5.6–6.7 and 2-hour postprandial BG <7.8 to 11.1 mmol/L) when risk of LGA was considered low. A recent meta-analysis has shown that this approach can result in a significant 50% reduction in LGA rate (p=0.0017, number needed to treat [NNT] 10 women with GDM) compared to standard care, without an increase in SGA rate (331), but caution should be used before extrapolation of these results to routine clinical practice. Indeed, it may be difficult to apply this flexible approach given the extreme glycemic targets that were used, the fact that routine determination of AC is not done or sufficiently reliable, and frequent ultrasounds may not be accessible to most centres. Further analyses are needed to estab-

lish safe stricter and relaxed glycemic targets that should be recommended for women with GDM to limit LGA and SGA rates.

Monitoring

Frequent SMBG is essential to guide therapy of GDM (331,333). Both fasting and postprandial testing are recommended to guide therapy in order to improve fetal outcomes (89,332). CGMS have been useful in determining previously undetected hyperglycemia, but it is not clear if it is cost effective (334–336). Recent randomized controlled trials suggest that CGM may be of benefit in the treatment of GDM. In a randomized trial, 340 women were randomized to undergo blinded 3-day CGM every 2 to 4 weeks from GDM diagnosis at 24 weeks GA or routine care with SMBG (337). Women using CGM had less glucose variability, less BG values out of the target range, as well as less preeclampsia, primary caesarean section and lower infant birthweight.

In a similar study of 106 women with GDM, given CGM from 24 to 28 weeks or 28 weeks to delivery, excess maternal weight gain was reduced in the CGM group compared to women doing only SMBG, especially in women who were treated with CGM earlier, at 24 weeks GA (338). A1C was lower in the CGM group but not statistically significantly different. More studies are needed to assess the benefits of CGM in this population.

In an effort to control their BG by diet, women with GDM may develop starvation ketosis. Older studies raised the possibility that elevated ketoacids may be detrimental to the fetus (94,339). While the clinical significance of these findings are questionable, it appears prudent to avoid ketosis.

eHealth medicine: Telehomecare and new technologies for glucose monitoring and healthy behaviour interventions

Use of new technologies and web-based platforms for BG monitoring in pregnant women with diabetes in Canada and worldwide is rapidly increasing. These initiatives allow for 2-way communication with women monitoring and transmitting their BG results in real time to health-care providers for feedback. Studies have demonstrated 38.0% (340) to 82.7% (341) reduction in face-to-face medical visits and decreased insulin use (340) in pregnant women using telehomecare in conjunction with conventional care, without an increase in maternal or perinatal complications. While 4 studies of GDM women (total n=272) have demonstrated comparable glycemic control and pregnancy outcomes (342–345), other studies with type 1 diabetes (346–348) and GDM (348) have shown improved glycemic control and pregnancy outcomes in the group using web-based programs compared to standard care. Enhanced patient empowerment and greater satisfaction with the care received are also reported in groups using new monitoring technology (340–343,345,348,349). However, generalizability of those studies is questionable as these studies were small, conducted in very specific settings and used different types of technologies and e-platforms. Furthermore, acceptance of these interventions by marginalized population subgroups (350) and in remote regions would also be important to determine. Finally, studies assessing cost effectiveness of these measures, both direct (health system resources utilization) and indirect (work absenteeism, parking, daycare fees) are needed.

Systematic reviews of the literature on the use of technology to support healthy behaviour interventions for healthy pregnant women (351) and women with GDM (352,353) showed that good quality trials in this area are few and research on this topic is in its infancy stage. This is evidenced by the focus on intervention acceptance measures, use of small sample sizes, lack of demonstration of causality and lack of examination of long-term effects or follow up.

In summary, new technologies and telehomecare programs have so far shown encouraging results to reduce medical visits and favour patient empowerment without increasing complication rates in pregnant women with diabetes. In an era of increased prevalence of GDM, well designed and sufficiently powered randomized controlled trials are needed to evaluate the effectiveness of technology as a tool for glucose management, healthy behaviour interventions and a way of relieving health-care system burden.

Pharmacological therapy

Insulin. If women with GDM do not achieve BG targets within 2 weeks of initiation of nutritional therapy and exercise, pharmacological therapy should be initiated (354,355). The use of insulin to achieve glycemic targets has been shown to reduce fetal and maternal morbidity (355,356). A variety of protocols have been used, with multiple daily injections (MDI) being the most effective (357). Insulin usually needs to be continuously adjusted to achieve glycemic targets. Although the rapid-acting bolus analogues aspart and lispro can help achieve postprandial targets without causing severe hypoglycemia (356–358), improvements in fetal outcomes have not been demonstrated with the use of aspart or lispro compared to regular insulin (356,357) *(see Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy: Pharmacological therapy)*. Glargine and detemir have primarily been assessed in women with pre-existing diabetes in pregnancy *(see Pre-Existing Diabetes (Type 1 and Type 2) in Pregnancy: Pharmacological therapy)*. Randomized trial evidence suggests levemir is safe and may afford less maternal hypoglycemia compared to neutral protamine hagedorn (NPH), while observational studies suggest that glargine, although theoretically less desirable, is also safe.

Other antihyperglycemic agents

Metformin. In several meta-analyses of randomized trials studying the use of metformin compared with insulin in women with gestational diabetes, women treated with metformin had less weight gain (359) and less pregnancy-induced hypertension compared to women treated with insulin (360–365). Infants of mothers using metformin had lower gestational age and less neonatal hypoglycemia. On the other hand, there was conflicting evidence regarding preterm birth, with some studies finding a significant increase with the use of metformin, while others did not. This finding was mainly demonstrated by the Metformin in Gestational diabetes (MiG) trial (366), where there was an increase in spontaneous preterm births rather than iatrogenic preterm births. The reason for this was unclear.

While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta. Results of The Offspring Follow Up of the Metformin in Gestational diabetes (MiG TOFU) trial, at 2 years, showed that the infants exposed to metformin have similar total fat mass but increased subcutaneous fat, suggesting a possible decrease in visceral fat compared to unexposed infants (367). In another follow-up study of infants exposed to metformin during pregnancies with gestational diabetes, children exposed to metformin weighed more at the age of 12 months, and were heavier and taller at 18 months, however, body composition was similar (368) as was motor, social and linguistic development. Studies looking at neurodevelopment showed similar outcomes between exposed and nonexposed infants at 2 years of age (369,370).

In summary, long-term follow up from 18 months to 2 years indicate that metformin exposure in-utero does not seem to be harmful with regards to early motor, linguistic, social, (368), metabolic (367,368) and neurodevelopmental (369,370) outcomes. Longer-term follow up is not yet available.

Glyburide. Glyburide has been shown to cross the placenta. In 2 meta-analyses of randomized trials studying the use of glyburide vs. insulin in women with GDM, glyburide was associated with

increased birthweight, macrosomia and neonatal hypoglycemia compared with insulin (361,362). In the same meta-analyses, compared to metformin, glyburide use was associated with increased maternal weight gain, birthweight, macrosomia and neonatal hypoglycemia (361,362). Therefore, the use of glyburide during pregnancy is not recommended as first- or second-line treatment, but may be used as third-line treatment if insulin is declined by the mother and metformin is either declined or insufficient to maintain good glycemic control.

Acarbose. There is only 1 small randomized trial looking at the use of acarbose in women with GDM. There was no difference in maternal/fetal outcomes compared to insulin although gastrointestinal side effects were increased (371).

Other antihyperglycemic agents. There is no human data on the use of DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors. The use of these noninsulin antihyperglycemic agents is not recommended during pregnancy.

Obstetrical Considerations in Women with Gestational Diabetes (See Section Entitled 'Obstetrical Considerations in Women with Pre-Existing Diabetes and Gestational Diabetes')

Intrapartum glucose management

The primary goal of intrapartum glucose management in women with gestational diabetes is to prevent neonatal hypoglycemia, which is thought to occur from the fetal hyperinsulinism caused by maternal hyperglycemia (372). Longer-term follow-up studies have found that infants with neonatal hypoglycemia had increased rates of neurological abnormalities at 18 months, especially if hypoglycemic seizures occurred or if hypoglycemia was prolonged (373,374) and at 8 years of age with deficits in attention, motor control and perception (375).

Risk of neonatal hypoglycemia is related to maternal BG levels

Maternal hyperglycemia during labour, even when produced for a few hours by intravenous fluids in mothers without diabetes, can cause neonatal hypoglycemia (376,377). Studies have generally been performed in mothers with pregestational diabetes or insulin-treated GDM. These have been observational with no randomized trials deliberately targeting different levels of maternal glycemia during labour. Most have found that there is a continuous relationship between mean maternal BG levels during labour and the risk of neonatal hypoglycemia with no obvious threshold. Authors have often chosen 2 levels within the range and shown that there is more hypoglycemia with the higher value, but the studies do not arrive at a common value and vary from <4.6 mmol/L to <8.0 mmol/L (378–387). By consensus, we suggest aiming for <7.0 mmol/L during labour and delivery.

Intrapartum insulin management

Insulin requirements tend to decrease intrapartum (385,386). There are very few studies (although many published protocols) that examine the best method of managing glycemia during labour (387,388). Given the lack of studies, there are no specific protocols that can be recommended to achieve the desired maternal BG levels during labour.

Postpartum

Breastfeeding. Women with GDM should be encouraged to breastfeed immediately after delivery and for at least 4 months postpartum, as this may contribute to the reduction of neonatal hypoglycemia (211) and offspring obesity (215), and prevent the development of metabolic syndrome and type 2 diabetes in the mother (214,389–397). Longer duration and more intense breastfeeding is associated with less diabetes in the mother with hazard ratios as low as 0.43 (395). Furthermore, offspring that are breastfed for at least 4 months have lower incidence of obesity and diabetes longer term (212). However, GDM is associated with either similar (189) or poor initiation rates (398) compared to those without diabetes, as well as poor continuation rates (189). Factors associated with cessation of breastfeeding before 3 months include breastfeeding challenges at home, return to work, inadequate support, caesarean section and lower socioeconomic status (399). In conclusion, women with GDM should be encouraged to breastfeed as long as possible as intensity and duration of nursing have both infant and maternal benefits (current recommendation by Canadian Paediatric Society is up to 2 years) (217), but more support is needed as this group is at risk for early cessation.

Long-term maternal risk of dysglycemia. With the diagnosis of GDM, there is evidence of impairment of both insulin secretion and action (400,401). These defects persist postpartum and increase the risk of impaired fasting glucose, IGT and type 2 diabetes (402,403). The cumulative risk increases markedly in the first 5 years and more slowly after 10 years (404,405). At 3 to 6 months postpartum, risks of dysglycemia are in the 16% to 20% range. While elevated FPG during pregnancy is a strong predictor of early development of diabetes (406–408), other predictors include age at diagnosis, use of insulin, especially bedtime insulin or oral agents, and more than 2 pregnancies (408–410). A1C at diagnosis of GDM is also a predictor of postpartum diabetes (408,411). Any degree of dysglycemia is associated with increased risk of postpartum diabetes (412). After 16 years, 40% of women with prior GDM will develop type 2 diabetes (413). Some women with GDM, especially lean women under 30 years of age who require insulin during pregnancy, progress to type 1 diabetes (414,415). Women with positive autoantibodies (anti-glutamic acid decarboxylase [anti-GAD], anti-insulinoma antigen 2 [anti- IA2]) are more likely to have diabetes by 6 months postpartum (416).

Postpartum testing is essential to identify women who continue to have diabetes, those who develop diabetes after temporary normalization and those at risk, including those with IGT. However, many women do not receive adequate postpartum follow up, and many believe they are not at high risk for diabetes (417–419). Only 14% to 50% return for postpartum testing (419–422) with annual follow-up rates of only 20% (423,424). Proactive contacts increased testing from 33% to 60% (425,426). Despite this finding, more work in this area is needed to improve uptake. One study revealed that, despite email reminders, absolute improvement was only 10% (427).

Women should be screened postpartum to determine their glucose status. Postnatal FBG has been the most consistently found variable in determining women at high risk for early postpartum diabetes (428). However, FPG alone will miss many women with some degree of abnormal glucose tolerance (429–431); therefore, a 75 g OGTT should be done between 6 weeks and 6 months postpartum. Some recent trials have shown that early postpartum testing (day 2 postpartum) may be as good at detecting diabetes as standard testing times; however, follow up in the standard testing group was poor. One study noted a 100% sensitivity and 94% specificity for diabetes detection but not as effective as identifying other forms of glucose abnormalities, and the sample size was small. If this can be confirmed in more rigorous trials, it may be useful to do early postpartum testing in women at high risk for type 2 diabetes or at high risk for noncompliance with follow up (432). A1C does not have the sensitivity to detect dysglycemia

postpartum (433) and, even combined with FBS, did not help improve its sensitivity (434,435).

Women should be counselled that the recurrence rate of GDM is high, from 30% to 84%, in subsequent pregnancies (436,437). Metabolic syndrome has been shown to be more prevalent in women with GDM (438–440) with rates as high as 23%, 3 times age-matched control using IADPSG criteria to diagnose GDM (441). Given the increased risk of CVD (OR 1.51) (442) with metabolic syndrome, consideration should be given to screening for all components of the metabolic syndrome in the postpartum care of women with GDM, especially if there is a family history (443,444). Education on healthy behaviour interventions to prevent diabetes and CVD should begin in pregnancy and continue postpartum (445,446). Awareness of physical activity for prevention of diabetes is low (447), and emphasis on targeted strategies that incorporate women's exercise beliefs may increase participation rates (448). Although 1 study showed women with prior gestational diabetes and IGT reduced their risk of developing diabetes with both a lifestyle intervention or metformin, these women were, on average, 12 years postpartum. More recent intervention studies of women with GDM alone who were closer to the time of delivery were often underpowered and compliance with the intervention was low.

The 2 largest randomized controlled trials to date were conflicting. The Mothers After Gestational Diabetes in Australia (MAGDA) study randomized 573 women within the first year postpartum to a group-based lifestyle intervention vs. standard care. After 1 year they found a 1 kg difference in weight and no difference in waist circumference or FBG (449). However, only 10% of women attended all the sessions, and 34% attended none. In another randomized controlled trial, 260 women were randomized to receive the Mediterranean diet and physical activity sessions for 10 weeks between 3 to 6 months postpartum, and then reinforcement sessions at 9 months, 1, 2 and 3 years. They found that significantly less women developed glycemic disorders in the intervention group (42% vs. 58%) (450). At 3 years, women in the intervention group had a lower BMI and better nutrition but similar rates of physical activity. However, engaging women to adopt health behaviours may be challenging soon after delivery. More studies are needed to explore interventions that may help this population reduce their risk.

Long-term metabolic impact of fetal exposure to maternal GDM. Observational studies have linked maternal GDM with poor metabolic outcomes in offspring (451). However, 3 systematic reviews (452–454) have concluded that maternal GDM is inconsistently or minimally associated with offspring obesity and overweight and this relationship is substantially attenuated or eliminated when adjusted for confounders. The HAPO offspring study extended their follow up to 5- to 7-year-olds and found that after adjustment for maternal BMI, higher maternal plasma glucose (PG) concentrations during pregnancy were not a risk for childhood obesity (455). In contrast, a recent cohort found an association between maternal FPG and offspring BMI at 7 years of age that persisted after adjustment for birth weight, socioeconomic status and maternal pre-pregnancy BMI (456). Current evidence fails to support the hypothesis that treatment of GDM reduces obesity and diabetes in offspring. Three follow-up studies of offspring whose mothers were in randomized controlled trials of GDM management found that treatment of GDM did not affect obesity at 4 to 5 years, 5 to 10 years or a mean age of 9 years (457–459). This follow up may be too short to draw conclusions about longer-term impact. However, it is interesting to note that the excess weight in offspring of women with diabetes in the observational work by Silverman et al (460) was evident by 5 years of age. Furthermore, a subanalysis of another trial follow-up study revealed that comparison by age at follow up 5 to 6 vs. 7 to 10 years old did not influence their findings (458).

Association between maternal diabetes and other long-term offspring outcomes, such as childhood academic achievement and autism spectrum disorders (ASD), have been explored in observational studies. Reassuringly, offspring of mothers with pre-existing type 1 diabetes had similar average grades when finishing primary school compared to matched controls (461). Associations between autism and different types of maternal diabetes during pregnancy have been inconsistent and usually disappear or are substantially attenuated after adjustment for potential confounders (462,463). Unspecified antihyperglycemic medications were either not associated with ASD (463) or not independently associated with ASD risk (462,463), but merit further investigation to assess if there are differences in the association between different types of antihyperglycemic agents and ASD.

Contraception after GDM. Women with prior GDM have numerous choices for contraception. Risk and benefits of each method should be discussed with each patient and same contraindications apply as in non-GDM women. Special attention should be given as women with GDM have higher risk of metabolic syndrome and, if they have risk factors, such as hypertension and other vascular risks, then IUD or progestin-only contraceptives should be considered (464). The effect of progestin-only agents on glucose metabolism and risk of type 2 diabetes in lactating women with prior GDM merits further study as in 1 population this risk was increased (464,465).

Planning future pregnancies. Women with previous GDM should plan future pregnancies in consultation with their health-care providers (466,467). Screening for diabetes should be performed prior to conception to assure normoglycemia at the time of conception (see Screening for Diabetes in Adults chapter, p. S16), and any glucose abnormality should be treated. In an effort to reduce the risk of congenital anomalies and optimize pregnancy outcomes, all women should take a folic acid supplement of 1.0 mg (467).

RECOMMENDATIONS

Pre-existing Diabetes

Preconception care

1. All women of reproductive age with type 1 or type 2 diabetes should receive ongoing counselling on reliable birth control, the importance of glycemic control prior to pregnancy, the impact of BMI on pregnancy outcomes, the need for folic acid and the need to stop potentially embryopathic drugs prior to pregnancy [Grade D, Level 4 (7)].

2. Women with type 2 diabetes with irregular menses/PCOS who lose significant weight or are started on metformin or a thiazolidinedione (TZD) should be advised that fertility may improve and be counselled regarding possible pregnancy and receive preconception counselling [Grade D, Consensus].

3. Before attempting to become pregnant, women with type 1 or type 2 diabetes should:
   a. Receive preconception counselling that includes optimal diabetes management, including nutrition, preferably in consultation with an interprofessional pregnancy team to optimize maternal and neonatal outcomes [Grade C, Level 3 (6,7,76,468)]
   b. Strive to attain a preconception A1C ≤7.0% (or A1C ≤6.5% if can safely be achieved) to decrease the risk of:
      i. Spontaneous abortion [Grade C, Level 3 (159)]
      ii. Congenital anomalies [Grade C, Level 3 (7,76,469,470)]
      iii. Preeclampsia [Grade C, Level 3 (471,472)]
      iv. Progression of retinopathy in pregnancy [Grade A, Level 1 for type 1 diabetes (25); Grade D, Consensus for type 2 diabetes]
      v. Stillbirth [Grade C, Level 3 (77)].
   c. Supplement their diet with multivitamins containing 1 mg of folic acid at least 3 months preconception and continuing until at least

12 weeks of gestation to prevent congenital anomalies [Grade D, Level 4 (14)]
   d. Discontinue medications that are potentially embryopathic, including any from the following classes:
      i. ACE inhibitors and ARBs
         1. Prior to conception in women with hypertension alone [Grade C, Level 3 (65–67)]
         2. Upon detection of pregnancy in women with CKD [Grade D, Consensus]
      ii. Statins [Grade D, Level 4 (473)].

4. Women on metformin and/or glyburide preconception may continue on these agents if glycemic control is adequate until pregnancy is achieved [Grade C, Level 3 (152,153)]. Women on other antihyperglycemic agents, should switch to insulin prior to conception as there are no safety data for the use of other antihyperglycemic agents in pregnancy [Grade D, Consensus].

Assessment and management of complications

5. Women should undergo an ophthalmological evaluation by a vision care specialist during pregnancy planning, the first trimester, as needed during pregnancy after that and, again, within the first year postpartum in order to identify progression of retinopathy [Grade B, Level 1 for type 1 diabetes (25); Grade D, Consensus for type 2 diabetes]. More frequent retinal surveillance during pregnancy as determined by the vision care specialist should be performed for women with more severe pre-existing retinopathy and poor glycemic control, especially those with the greatest anticipatory reductions in A1C during pregnancy, in order to reduce progression of retinopathy [Grade B, Level 1 for type 1 diabetes (25,27); Grade D, Consensus for type 2 diabetes].

6. Women with albuminuria or CKD should be followed closely for the development of hypertension and preeclampsia [Grade D, Consensus].

Management in pregnancy

7. Once pregnant, women with pre-existing diabetes should receive care by an interprofessional diabetes health-care team, including diabetes educators (nurse and dietitian), obstetrical care provider, and physician/nurse practitioner, with expertise in diabetes and pregnancy to minimize maternal and fetal risks [Grade C, Level 3 (7)].

8. Once pregnant, women with type 2 diabetes should be switched to insulin for glycemic control [Grade D, Consensus]. Noninsulin antihyperglycemic agents should only be discontinued once insulin is started [Grade D, Consensus].

9. Pregnant women with pre-existing diabetes should:
   a. Receive an individualized insulin regimen and glycemic targets typically using intensive insulin therapy by basal-bolus injection therapy [Grade A, Level 1B, for type 1 diabetes (73,129); Grade A, Level 1, (129) for type 2 diabetes] or CSII (insulin pump) [Grade C, Level 3 (147) for type 1 diabetes]
   b. Strive for target BG values [Grade D, Consensus for all values]:
      i. Fasting and preprandial <5.3 mmol/L
      ii. 1 hour postprandial <7.8 mmol/L
      iii. 2 hours postprandial <6.7 mmol/L
   c. Aim for an A1C of ≤6.5% during pregnancy (≤6.1% if possible), if can be achieved safely, to lower the risk of late stillbirth and infant death [Grade D, Level 4 (77)]
   d. Be prepared to raise BG and A1C targets in the presence of severe hypoglycemia during pregnancy [Grade D, Consensus]
   e. Perform SMBG, both pre- and postprandially, to improve pregnancy outcomes [Grade C, Level 3 (76)].

10. Health-care providers should discuss appropriate weight gain at the initial visit and regularly throughout pregnancy [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be individualized based on the Institute of Medicine guidelines by pre-pregnancy BMI to lower the risk of LGA infants [Grade B, Level 2 (120,121)].

11. Aspart, lispro or glulisine may be used in women with pre-existing diabetes to improve postprandial BG [Grade C, Level 2 (104) for aspart; Grade C, Level 3 (132,133,135) for lispro; Grade D, Level 4 (137) for glulisine] and reduce the risk of severe maternal hypoglycemia [Grade C, Level 3 (135) for aspart and lispro; Grade D, Consensus for glulisine] compared with human regular insulin.

12. Detemir [Grade B, Level 2 (474)] or glargine [Grade C, Level 3 (142)] may be used in women with pre-existing diabetes as an alternative to NPH and is associated with similar perinatal outcomes.

13. Women with pre-existing diabetes should start ASA 81* mg daily at 12–16 weeks' gestation to reduce the risk of preeclampsia [Grade D, Level 4 (48)]. *81 mg is commonly used in Canada due to its commercial availability, but the optimal dose has yet to be determined. Recent evidence suggests that higher dosage regimens might provide additional efficacy.

14. Women with type 1 and insulin-treated type 2 diabetes who receive antenatal corticosteroids to improve fetal lung maturation should follow a protocol that increases insulin doses proactively to prevent hyperglycemia [Grade D, Level 4 (157)] and DKA [Grade D, Consensus].

15. Women with type 1 diabetes in pregnancy should be offered use of CGM to improve glycemic control and reduce neonatal complications [Grade B, Level 2 (113)].

Fetal surveillance and timing of delivery

16. In women with pre-existing diabetes, assessment of fetal well-being should be initiated at 30–32 weeks' gestation and performed weekly starting at 34–36 weeks' gestation and continued until delivery [Grade D, Consensus]. Earlier onset and/or more frequent fetal health surveillance is recommended in those considered at highest risk [Grade D, Consensus].

17. In women with uncomplicated pre-existing diabetes, induction should be considered between 38–39 weeks of gestation to reduce risk of stillbirth [Grade D, Consensus]. Induction prior to 38 weeks of gestation should be considered when other fetal or maternal indications exist, such as poor glycemic control [Grade D, Consensus]. The potential benefit of early term induction needs to be weighed against the potential for increased neonatal complications.

Intrapartum glucose management

18. Women should be closely monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0–7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus].

19. CSII (insulin pump) may be continued in women with pre-existing diabetes during labour and delivery if the women or their partners can independently and safely manage the insulin pump and they choose to stay on the pump during labour and delivery [Grade C, Level 3 (172) for type 1 diabetes; Grade D, Consensus for type 2 diabetes].

Postpartum

20. Insulin doses should be decreased immediately after delivery below prepregnant doses and titrated as needed to achieve good glycemic control [Grade D, Consensus].

21. Women with pre-existing diabetes should have frequent blood glucose monitoring in the first days postpartum, as they have a high risk of hypoglycemia [Grade D, Consensus].

22. For women with pre-existing diabetes, early neonatal feeding should be encouraged immediately postpartum to reduce neonatal hypoglycemia [Grade C, Level 3 (211)]. Breastfeeding should be encouraged to reduce offspring obesity [Grade C, Level 3 (215)] and for a minimum of 4 months to reduce the risk of developing diabetes [Grade C, Level 3 (212)]. Women with pre-existing diabetes should receive assistance and counselling on the benefits of breastfeeding, in order to improve breastfeeding rates, especially in the setting of maternal obesity [Grade D, Consensus].

23. Women with type 1 diabetes should be screened for postpartum thyroiditis with a TSH test at 2–4 months postpartum [Grade D, Consensus].

24. Metformin and/or glyburide may be used during breastfeeding [Grade C, Level 3 (203) for metformin; Grade D, Level 4 (204) for glyburide]. Other noninsulin antihyperglycemic agents should not be used during breastfeeding as safety data do not exist for these agents [Grade D, Consensus].

Gestational Diabetes

Prevention

25. In women at high risk for GDM based on pre-existing risk factors, nutrition counselling should be provided on healthy eating and prevention of

excessive gestational weight gain in early pregnancy, ideally before 15 weeks of gestation, to reduce the risk of developing GDM [Grade B, Level 2 (225,227)].

Screening and Diagnosis

26. Women identified as being at high risk for type 2 diabetes should be offered earlier screening with an A1C test at the first antenatal visit to identify diabetes which may be pre-existing [Grade D, Consensus]. For those women with a hemoglobinopathy or renal disease, the A1C test may not be reliable and screening should be performed with an FPG [Grade D, Consensus]. If the A1C is ≥6.5% or the FPG is ≥7.0 mmol/L, the woman should be considered to have diabetes in pregnancy and the same management recommendations for pre-existing diabetes should be followed [Grade D, Consensus].
    a. If the initial screening is performed before 24 weeks of gestation and is negative, the woman should be rescreened as outlined in recommendations 28 and 29 between 24–28 weeks of gestation [Grade D, Consensus].

27. All pregnant women not known to have pre-existing diabetes should be screened for GDM at 24–28 weeks of gestation [Grade C, Level 3 (475)].

28. The preferred approach for the screening and diagnosis of GDM at 24–28 weeks is the following [Grade D, Consensus]:
    a. Screening for GDM should be conducted using the 50 g GCT administered in the nonfasting state with PG glucose measured 1 hour later [Grade D, Level 4 (272)]. A PG ≥7.8 mmol/L at 1 hour is a positive screen and is an indication to proceed to the 75 g OGTT [Grade C, Level 2 (268)]. A PG ≥11.1 mmol/L is diagnostic of gestational diabetes and does not require a 75 g OGTT for confirmation [Grade D, Level 4 (272)]
    b. If the GCT screen is positive, a 75 g OGTT should be performed as the diagnostic test for GDM using 1 of the following criteria:
        i. Fasting PG ≥5.3 mmol/L OR
        ii. 1 hour PG ≥10.6 mmol/L OR
        iii. 2 hours PG ≥9.0 mmol/L [Grade B, Level 1 (273)].

29. An alternative approach to screen and diagnose GDM is the 1-step approach: a 75 g OGTT should be performed (with no prior screening 50 g GCT) as the diagnostic test for GDM using 1 of the following criteria:
    a. Fasting PG ≥5.1 mmol/L OR
    b. 1 hour PG ≥10.0 mmol/L OR
    c. 2 hours PG ≥8.5 mmol/L [Grade B, Level 1 (273)].

Management during pregnancy

30. Women with GDM should:
    a. To improve pregnancy outcomes, strive for target BG values:
        i. Fasting and preprandial <5.3 mmol/L [Grade B, Level 2 (85,88)]
        ii. 1 hour postprandial <7.8 mmol/L [Grade D, Level 4 (87)]
        iii. 2 hours postprandial BG <6.7 mmol/L [Grade B, Level 2 (85)]
    b. Perform SMBG, both fasting and postprandially, to improve pregnancy outcomes [Grade B, Level 2 (89)]
    c. For women on insulin therapy, maintain BG levels >3.7 mmol/L [Grade D, Consensus].

31. Health-care providers should discuss appropriate weight gain and healthy lifestyle interventions regularly throughout pregnancy [Grade D, Consensus]. Recommendations for weight gain for women with GDM should be individualized based on Institute of Medicine guidelines by pre-pregnancy BMI to prevent excessive gestational weight gain and reduce the risk of LGA [Grade B, Level 2 (297,299)], macrosomia and caesarean sections [Grade B, Level 2 (296,297)].

32. Nutritional counselling by a registered dietitian should be provided to women with GDM to help them achieve their nutrition, weight and blood glucose goals [Grade D, Level 4 (306)]. Women with GDM should be encouraged to eat a healthy diet for pregnancy and to replace high-GI foods with low-GI foods to reduce the need for insulin initiation and decrease birth weight [Grade C, Level 3 (315)].

33. If women with GDM do not achieve glycemic targets within 1–2 weeks with nutritional therapy and physical activity, pharmacologic therapy should be initiated [Grade D, Consensus].
    a. Insulin in the form of basal-bolus injection therapy may be used as first-line therapy [Grade A, Level 1 (129) for insulin]
    b. Rapid-acting analogue insulin aspart, lispro or glulisine may be used over regular insulin for postprandial glucose control, although perinatal outcomes are similar [Grade B, Level 2 (356,357) for aspart and lispro; Grade D, Consensus for glulisine]
    c. Metformin may be used as an alternative to insulin [Grade A, Level 1A (362) for metformin]; however, women should be informed that metformin crosses the placenta, longer-term studies are not yet available, and the addition of insulin is necessary in approximately 40% to achieve adequate glycemic control [Grade D, Consensus].

34. In women with GDM who decline insulin and do not tolerate or are inadequately controlled on metformin, glyburide may be used [Grade B, Level 2 (362)].

Fetal surveillance and timing of delivery in GDM

35. Increased frequency of fetal assessment should be considered in women with GDM that is poorly controlled and/or associated with comorbid conditions [Grade D, Consensus].

36. Women with GDM can be offered induction of labour between 38–40 weeks' gestation to potentially reduce the risk of stillbirth [Grade D, Consensus] and the risk of caesarean section [Grade C, Level 2 (167,169)]. Earlier or later induction of labour should be considered based on glycemic control and the presence or absence of other comorbid conditions [Grade D, Consensus].

Intrapartum glucose management

37. Women with GDM should be monitored during labour and delivery, and maternal blood glucose levels should be kept between 4.0–7.0 mmol/L in order to minimize the risk of neonatal hypoglycemia [Grade D, Consensus].

Postpartum

38. Women with GDM should be encouraged to breastfeed immediately after delivery in order to avoid neonatal hypoglycemia [Grade D, Consensus] and to continue for at least 3–4 months postpartum in order to prevent childhood obesity [Grade C, Level 3 (476)] and diabetes in the offspring [Grade D, Level 4 (476)] and to reduce risk of type 2 diabetes and hypertension in the mother [Grade C, Level 3 (391,395,396,476)].

39. Women should be screened with a 75 g OGTT between 6 weeks to 6 months postpartum to detect prediabetes and diabetes [Grade D, Consensus]. Methods to improve postpartum testing, such as phone calls or email reminders to women with a history of GDM, should be employed to improve screening rates [Grade C, Level 3 (425)].

40. In women who were diagnosed with diabetes in early pregnancy based on A1C (see recommendation 29), if ongoing hyperglycemia is not evident postpartum, a confirmatory test for diabetes with a FPG or 75 g OGTT should be done at 6 to 8 weeks' postpartum [Grade D, Consensus].

41. Women with prior GDM should receive counselling regarding healthy behaviour interventions to reduce the recurrence rate in subsequent pregnancies and reduce their increased risk of type 2 diabetes [Grade C, Level 3 (445,446)].

42. In women with prior GDM who have IGT on postpartum screening, healthy behaviour interventions with or without metformin can be used to prevent/delay the onset of diabetes [Grade B, Level 2 (477,478)].

Abbreviations:
A1C, glycated hemoglobin; *AC*, abdominal circumference; *ACE*, angiotensin-converting enzyme; *aOR*; adjusted odds ratio; *ARB*, angiotensin II receptor blocker; *ASD*, autism spectrum disorder; *BG*, blood glucose; *BMI*, body mass index; *BP*, blood pressure; *CBG*; capillary blood glucose; *CGM*, continuous glucose monitoring; *CKD*, chronic kidney disease; *CrCl*; creatinine clearance; *CSII*; continuous subcutaneous insulin infusion; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DHC*, diabetes health-care; *DKA*, diabetic ketoacidosis; *DPP-4*, dipeptidyl peptidase-4; *FBG*, fasting blood glucose; *GCT*, glucose challenge test; *GDM*, gestational diabetes; *GLP-1*, glucagon-like polypeptide-1; *GWG*, gestational weight gain; *GI*, glycemic index; *IGT*, impaired glucose tolerance; *IOL*, induction of labour; *IOM*, Institute of Medicine; *IUD*, intra-uterine device; *LDL-cholesterol*, low-density lipoprotein cholesterol; *LGA*, large for gestational age; *MDI*, multiple daily injections; *MI*, myocardial infarct; *NICU*, neonatal intensive care unit; *NNT*, number needed to treat; *NPH*, neutral protamine Hagedorn;

OGTT, oral glucose tolerance test; *PCOS*, polycystic ovarian syndrome; *PG*, plasma glucose; *RAAS*; renin angiotensin aldosterone system; *RR*, relative risk; *SD*, standard deviation; *SGA*, small for gestational age; *SGLT2*, sodium-glucose cotransporter-2; *SMBG*, self-monitoring of blood glucose; *TSH*, thyroid-stimulating hormone; *TZD*, thiazolidinedione.

Other Relevant Guidelines

Screening for Diabetes in Adults, p. S16
Organization of Diabetes Care, p. S27
Type 2 Diabetes and Indigenous Peoples, p. S296

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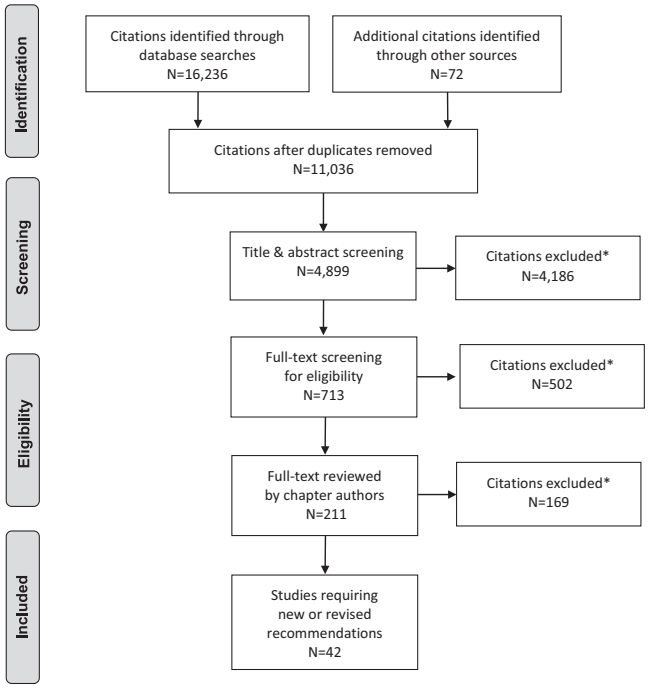
Literature Review Flow Diagram for Chapter 36: Diabetes and Pregnancy



*Excluded based on: population, intervention/exposure, comparator/control or study design

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2018 Clinical Practice Guidelines

Diabetes in Older People

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Diabetes in older people is distinct from diabetes in younger people and the approach to therapy should be different. This is especially true in those who have functional dependence, frailty, dementia or who are at end of life. This chapter focuses on these individuals. Personalized strategies are needed to avoid overtreatment of the frail elderly.
- In the older person with diabetes and multiple comorbidities and/or frailty, strategies should be used to strictly prevent hypoglycemia, which include the choice of antihyperglycemic therapy and a less stringent glycated hemoglobin (A1C) target.
- Sulphonylureas should be used with caution because the risk of hypoglycemia increases significantly with age.
- DPP-4 inhibitors should be used over sulfonylureas because of a lower risk of hypoglycemia.
- Long-acting basal analogues are associated with a lower frequency of hypoglycemia than intermediate-acting or premixed insulin in this age group.

KEY MESSAGES FOR OLDER PEOPLE WITH DIABETES

- No two older people are alike and every older person with diabetes needs a customized diabetes care plan. What works for 1 individual may not be the best course of treatment for another. Some older people are healthy and can manage their diabetes on their own, while others may have 1 or more diabetes complications. Others may be frail, have memory loss and/or have several chronic diseases in addition to diabetes.
- Based on the factors mentioned above, your diabetes health-care team will work with you and your caregivers to select target blood glucose and glycated hemoglobin (A1C) levels, appropriate glucose-lowering medications, and a program for screening and management of diabetes-related complications.

Introduction

This guideline refers primarily to type 2 diabetes in the older person. There is limited information on the management of type 1 diabetes in the elderly, but this is included wherever appropriate. The definition of "older" varies, with some studies defining the elderly population as ≥60 years of age. Administrative guidelines frequently classify people >65 years of age as older. Although there is no uniformly agreed-upon definition of older, it is generally accepted that this is a concept that reflects an age continuum starting sometime around age 70 and is characterized by a slow, progressive impairment in function that continues until the end of life (1). There are many people with type 2 diabetes who are over the age of 70 who are otherwise well, functionally independent/not frail and have at least a decade of healthy life expectancy. These people should be treated to targets and with therapies described elsewhere in this guideline (see Targets for Glycemic Control chapter, p. S42 and Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter, p. S88). This chapter focuses on older people who do not fall into any or all of those categories. Decisions regarding therapy should be made on the basis of age/life expectancy and the person's functional status. Where possible, evidence is based on studies where either the main focus was people over the age of 70 years or where a substantial subgroup, specifically reported, were in this age group.

Diagnosis and Screening

As noted in the Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome chapter, p. S10, glycated hemoglobin (A1C) can be used as a diagnostic test for type 2 diabetes in adults. Unfortunately, normal aging is associated with a progressive increase in A1C, and there can be a significant discordance between glucose-based and A1C-based diagnosis of diabetes in this age group, a difference that is accentuated by race and gender (2) (see Monitoring Glycemic Control chapter, p. S47). Pending further studies to define the role of A1C in the diagnosis of diabetes in the elderly, other tests may need to be considered in some older people, especially where the elevation in A1C is modest (i.e. 6.5% to 7.0%). Because they are complementary, we recommend screening with both a fasting plasma glucose and an A1C in older people.

Screening for diabetes may be warranted in select individuals. In the absence of positive intervention studies on morbidity or mortality in this population, the decision about screening for diabetes should be made on an individual basis. Screening is unlikely to be beneficial in most people over the age of 80.

Reducing the Risk of Developing Diabetes

Healthy behaviour interventions are effective in reducing the risk of developing diabetes in older people at high risk for the development of the disease (3). Acarbose (4), rosiglitazone (5) and pioglitazone (1,6) also are effective in preventing diabetes in high-risk

Conflict of interest statements can be found on page S290.

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elderly. Metformin may not be effective (3). Since several of these drugs have significant toxicity in the older adult (see below) and since there is no evidence that preventing diabetes will make a difference in outcomes in these people, there would appear to be little justification for drug therapy to prevent diabetes in older adults.

Management

Organization of care

As interprofessional interventions specifically designed for older adults have been shown to improve glycemic control, referrals to diabetes health-care (DHC) teams should be facilitated (7–9). Pay-for-performance programs improve a number of quality indicators in this age group (10,11). Telemedicine case management and web-based interventions can improve glycemic control, lipids, blood pressure (BP), psychosocial well-being and physical activity; reduce hypoglycemia and ethnic disparities in care; and allow for detection and remediation of medically urgent situations, as well as reduce hospitalizations (12–21). A pharmaceutical care program (e.g. monitoring of symptoms, medication counselling, facilitating communications with physicians/nurse practitioners by pharmacists) can significantly improve medication compliance, as well as the control of diabetes and its associated risk factors (22,23) (see Organization of Care chapter, p.S27).

Self-management education and support

Self-management education and support programs are a vital aspect of diabetes care, particularly for older adults who may require additional education and support in light of other chronic conditions and polypharmacy (24). Recently, a population-based cohort study of older adults (≥65 years of age) living in Ontario found that attendance at a diabetes education program was associated with better quality of care, and better participation relating to education utilization and retinopathy screening (25). A review of diabetes self-management programs for older adults ≥65 years of age, identified that programs that emphasized tailored education and support, or psychological support resulted in greater reductions in A1C, when compared to group-setting education, review and feedback monitoring, or medical management (24) (see Self-Management Education and Support chapter, p. S36).

In the absence of frailty, intensive healthy behaviour interventions may be applicable for appropriate older adults. A 1-year intensive self-management healthy behaviours program (calorie reduction and increased physical activity) was associated with a statistically significant benefit on weight reduction, increased high-density lipoprotein cholesterol (HDL-C), decreased A1C and reduced waist circumference in older adults ranging from 65 to 76 years of age (26). Diabetes self-management programs with access to geriatric teams (i.e. geriatricians, diabetes nurse educators, registered dietitians) can further improve glycemic control and self-care behaviours when compared to usual care, by assessing barriers and providing strategies and opportunities for ongoing support between clinic visits (27).

Targets for glycemic control

The same glycemic targets apply to otherwise healthy older adults as to younger people with diabetes (see below), especially if these targets can be obtained using antihyperglycemic agents associated with low risk of hypoglycemia (see Targets for Glycemic Control chapter, p. S42). In older people with diabetes of several years' duration and established complications, intensive control reduced the risk of microvascular events but did not reduce cardiovascular (CV) events or overall mortality (28–31). Overall mortality was increased in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study. Therefore, in older people with longstanding diabetes and multiple comorbidities, intensive glycemic control is not advisable. While the initial report of the ACCORD-MIND substudy suggested that intensive control preserved brain volume but did not alter cognitive outcomes, subsequent follow up found no impact on either parameter (32). However, better glycemic control may be associated with less disability and better function (33,34). In cohort studies, it has been demonstrated that the best survival is present in elderly people with an A1C between 7.0% to 8.0%, and values above and below this range are associated with increased mortality (35,36). Table 1 outlines glycemic targets for the elderly across the health spectrum.

Recently, an A1C-derived average blood glucose value has been developed and offered to people with diabetes and health-care providers as a better way to understand glycemic control. While this is a valuable parameter in younger people, this variable and A1C may not accurately reflect continuous glucose monitoring (CGM) measured glucose values or glycemic variability in the older adult (37).

It has been suggested that postprandial glucose values are a better predictor of outcome in older people with diabetes than A1C or preprandial glucose values. Older people with type 2 diabetes who have survived an acute myocardial infarct (MI) may have a lower risk for a subsequent CV event with targeting of postprandial vs. fasting/preprandial glycemia (38). In people with diabetes with equivalent glycemic control, greater variability of glucose values is associated with worse cognition (39).

Recent international guidelines have focused on functional status as a key factor in determining the target A1C in older people with diabetes (Table 2). There is an acceptance that as functional

Table 1
Glycemic targets in older people with diabetes

Status	Functionally independent	Functionally dependent	Frail and/or with dementia	End of life
Clinical Frailty Index*	1–3	4–5	6–8	9
A1C target *Low-risk hypoglycemia* (i.e. therapy does **not** include insulin or SU)	≤7.0%	<8.0%	<8.5%	A1C measurement not recommended. Avoid symptomatic hyperglycemia or any hypoglycemia.
A1C target *Higher-risk hypoglycemia* (i.e. therapy includes insulin or SU)		7.1–8.0%	7.1–8.5%	
CBGM				
Preprandial	4–7 mmol/L	5–8 mmol/L	6–9 mmol/L	Individualized
Postprandial	5–10 mmol/L	<12 mmol/L	<14 mmol/L	

A1C, glycated hemoglobin; *CBGM*, capillary blood glucose monitoring; *SU*, sulfonylurea.
* Clinical Frailty Score (1 - very fit to 9 - terminally ill). Please see Figure 1.

Table 2
Guideline recommendations for key clinical outcomes for older people with diabetes from Diabetes Canada (DC), American Diabetes Association (ADA) and International Diabetes Federation (IDF)

Measure	ADA	DC	IDF
A1C	Healthy: <7.5% Complex/Intermediate: <8.0% Very Complex/Poor Health: <8.5%	Functionally independent: ≤ 7.0% Functionally dependent: 7.1–8.0% Frail and/or dementia: 7.1–8.5% End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia.	Functionally independent: 7.0%–7.5% Functionally dependent: 7.0%–8.0% Sub-level frail: <8.5% Sub-level dementia: <8.5% End of life: avoid symptomatic hyperglycemia
Blood Pressure	Healthy: <140/80 mmHg Complex/Intermediate: <140/80 mmHg Very Complex/Poor Health: <150/90 mmHg	Functionally independent with life expectancy >10 years: <130/80 mmHg Functionally dependent, orthostasis or limited life expectancy: individualize BP targets	Functionally independent: <140/90 mmHg Functionally dependent: <140/90 mmHg Sub-level frail: <150/90 mmHg Sub-level dementia: <140/90 mmHg End of life: strict BP control may not be necessary
LDL-C	<1.8 mmol/L	<2.0 mmol/L or >50% reduction from baseline	<2.0 mmol/L and adjusted based on CV risk

Adapted from ADA (42) and IDF (40).
A1C, glycated hemoglobin; *BP*; blood pressure; *CV*, cardiovascular; *LDL-C*, low density lipoprotein cholesterol.

independence is lost and/or life expectancy shortens, the benefit of lower glycemic targets is diminished and the risk of hypoglycemia increases (40–42). Therefore, it is functional status and life expectancy, rather than age itself, that helps determine glycemic targets, including A1C.

Frailty

Diabetes is a marker of reduced life expectancy and functional impairment in the older person. People with diabetes develop disability at an earlier age than people without diabetes and they spend more of their remaining years in a disabled state (43,44). "Frailty" is a widely used term associated with aging and disability that denotes a multidimensional syndrome that gives rise to increased vulnerability. Frailty may have a biological basis and appears to be a distinct clinical syndrome. Many definitions of frailty have been proposed. The most commonly applied definition (Fried's Frailty Phenotype) suggests that a person is frail when 3 or more of the following criteria are present: unintentional weight loss (>4.5 kg in the past year), self-reported exhaustion, weakness (diminished grip strength), slow walking speed and low physical activity (45). Progressive frailty has been associated with reduced function and increased mortality. Frailty increases the risk of diabetes, and older people with diabetes are more likely to be frail (46,47). When frailty occurs, it is a better predictor of complications and death in older people with diabetes than chronological age or burden of comorbidity (48).

The Clinical Frailty Scale, developed by Rockwood et al, has demonstrated validity as a 9-point scale from 1 (very fit) to 9 (terminally ill), which can help to determine which older people are frail (49) (Figure 1). In people with multiple comorbidities, a high level of functional dependency and limited life expectancy (i.e. frail people), decision analysis suggests that the benefit of intensive glycemic control is likely to be minimal (50). From a clinical perspective, the decision to offer more or less stringent glycemic control should be based on the degree of frailty. People with moderate or more advanced frailty (Figure 1) have a reduced life expectancy and should not undergo stringent glycemic control. When attempts are made to improve glycemic control in these people, there are fewer episodes of significant hyperglycemia but also more episodes of severe hypoglycemia (51).

Monitoring glycemic control

The same general principles pertain to self-monitoring of blood glucose (SMBG) in older people, as they do for any person with diabetes (Monitoring Glycemic Control chapter, p. S47). The person with diabetes, or family or caregiver must have the knowledge and skills to use a home blood glucose monitor and record the results in an organized fashion. Additionally, the person with diabetes, and/or members of the health-care team, must be willing to review and act upon the SMBG results, in addition to the A1C results. In selected cases, continuous glucose monitoring (CGM) may be employed to determine unexpected patterns of hypoglycemia or hyperglycemia, which may result in significant changes in therapy (see below). Since the correlation between A1C values and CGM-derived mean glucose values is much less in the elderly than younger patient populations, the 2 measures may be used in a complementary manner to assess glycemic control in the future (37).

Particularly relevant to the older adult is the fact that glucose monitoring is the only way to confirm, and appropriately treat, hypoglycemia. Therefore, for older people treated with sulfonylureas, meglitinides and/or insulin, the ability to obtain SMBG at the time of symptoms consistent with hypoglycemia is essential. On the other hand, monitoring is often conducted when it is not required. Regular monitoring is generally not needed in well-controlled subjects on antihyperglycemic agents that rarely cause hypoglycemia (see Monitoring Glycemic Control chapter, p. S47).

Unfortunately, aging is a risk factor for severe hypoglycemia with efforts to intensify therapy (52). Recent data suggests that a substantial number of clinically complex older people have tight glycemic control, which markedly increases their risk of hypoglycemia (53). Asymptomatic hypoglycemia, as assessed by CGM, is frequent in this population (54). This increased risk of hypoglycemia appears to be due to an age-related reduction in glucagon secretion, impaired awareness of hypoglycemic warning symptoms and altered psychomotor performance, which prevents the person from taking steps to treat hypoglycemia (55–57). Although it has been assumed that less stringent A1C targets may minimize the risks of hypoglycemia, a recent study using CGM suggests that older people with higher A1C levels still have frequent episodes of prolonged asymptomatic hypoglycemia (58). If these data are replicated in subsequent studies, the assumptions underlying higher A1C targets for functionally impaired people with diabetes will need to be revisited.

The consequences of a moderate-to-severe hypoglycemic episode could include a fall and injury, seizure or coma, or a CV event (59). A1C values <6.5% and >8.0% are associated with an increased risk of fractures (60). Episodes of severe hypoglycemia may increase the risk of dementia (61), although this is controversial (62). Conversely, cognitive dysfunction in older people with diabetes has clearly been identified as a significant risk factor for the development of severe hypoglycemia (62–64).

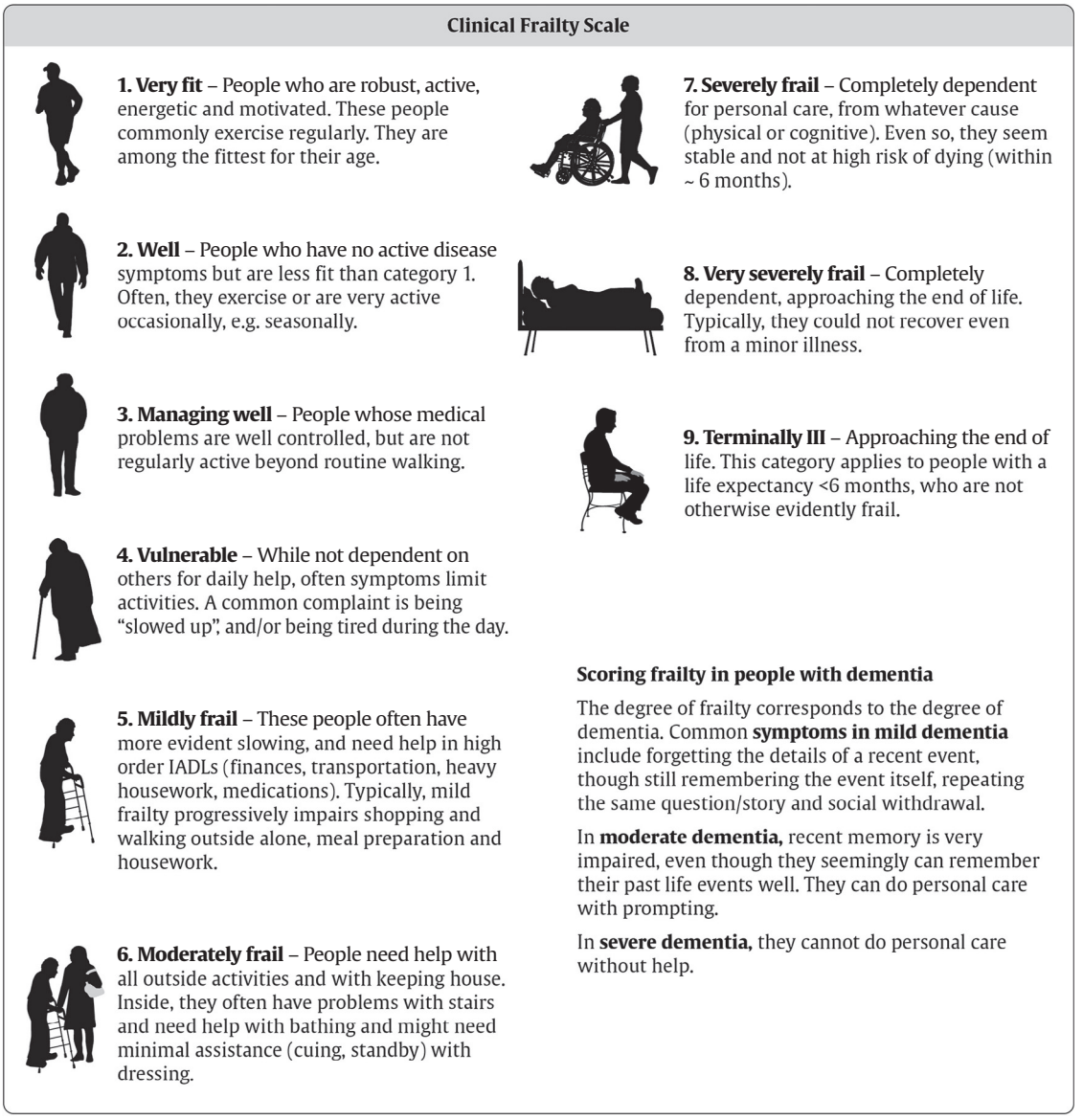

Figure 1. Clinical frailty scale. Adapted with permission from Moorhouse P, Rockwood K. Frailty and its quantitative evaluation (49).

Nutrition and physical activity

Nutrition education can improve metabolic control in ambulatory older people with diabetes (65). Although nutrition education is important, weight loss may not be, since moderate obesity is associated with a lower mortality in this population (66). Amino acid supplementation may improve glycemic control and insulin sensitivity in these people, although this is controversial (67,68).

Older women with diabetes have a greater decline in walking speed when compared to a control group without diabetes (69). In the older population with diabetes, higher levels of physical activity are associated with greater survival (70). Physical training programs can be successfully implemented in older people with diabetes, although comorbid conditions may prevent aerobic physical training in many patients, and increased activity levels may be difficult to sustain. Prior to instituting an exercise program, elderly people should be carefully evaluated for underlying CV or musculoskeletal problems that may preclude such programs. Aerobic exercise improves arterial stiffness and baroreflex sensitivity, both surrogate markers of increased CV morbidity and mortality (71,72). While the effects of aerobic exercise programs on glucose and lipid metabolism are inconsistent (73–75), resistance training has been shown to result in modest improvements in glycemic control, as well as improvements in strength, body composition and mobility (76–80). Exercise programs may also reduce the risk of falls and improve balance in older people with diabetes with neuropathy (81,82).

Unfortunately, it appears difficult to maintain these healthy behaviour changes outside of a supervised setting (83).

Noninsulin antihyperglycemic agents

In lean older people with type 2 diabetes, the principal metabolic defect is impairment in glucose-induced insulin secretion (84). Initial therapy for these individuals could include agents that stimulate insulin secretion without causing hypoglycemia, such as dipeptidyl peptidase-4 (DPP-4) inhibitors. In older people with obesity and type 2 diabetes, the principal metabolic defect is resistance to insulin-mediated glucose disposal, with insulin secretion being relatively preserved (85–87). Initial therapy for older people

with obesity and diabetes could involve agents that improve insulin resistance, such as metformin.

There have been no randomized trials of metformin in the older person with diabetes, although clinical experience suggests it is an effective agent. Metformin may reduce the risk of cancer in older people with diabetes (88,89). There is an association between metformin use and lower vitamin B12 levels, and monitoring of vitamin B12 should be considered in older people on this drug (90–92). Alpha-glucosidase inhibitors are modestly effective in older people with diabetes, but a substantial percentage of individuals cannot tolerate them because of gastrointestinal side effects (93–96). Thiazolidinediones (TZDs) are effective agents, but are associated with an increased incidence of edema and congestive heart failure (CHF) in older people (97–100). Rosiglitazone, but not pioglitazone, may increase the risk of CV events and death (101–104). These agents also increase the risk of fractures in women (97,104–106). When used as monotherapy, they are likely to maintain glycemic targets for a longer time than metformin or glyburide (100). Interestingly, drugs that increase insulin sensitivity, such as TZDs and metformin, may attenuate the progressive loss in muscle mass that occurs in older people with diabetes and contributes to frailty (107).

Sulphonylureas should be used with great caution because the risk of severe hypoglycemia increases substantially with age (108,109) and appears to be higher with glyburide (110–112). Gliclazide and glimepiride are preferred over glyburide in the elderly because they are associated with a lower frequency of hypoglycemia and CV events (113–119). A long-acting formulation of gliclazide resulted in equivalent glycemic control and the same frequency of hypoglycemic events as regular gliclazide in the older adult (115), and appears to result in a lower frequency of hypoglycemic events than glimepiride (116). Meglitinides (repaglinide and nateglinide) are associated with a lower frequency of hypoglycemia in the older person compared to glyburide (120–122) and may be considered in individuals with irregular eating habits.

DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) are similarly effective and safe in young and older people with diabetes, cause minimal hypoglycemia when used alone (or with metformin) and do not result in weight gain (123–132). Large numbers of older people have been enrolled in studies of these drugs, including those over 75 and with multiple comorbidities. When compared to sulfonylureas in monotherapy or in combination with metformin, DPP-4 inhibitors result in equivalent glycemic control but result in much lower rates of hypoglycemia (133–137). When added to insulin, linagliptin may improve glycemic control without increasing the risk of hypoglycemia (138). Saxagliptin, alogliptin and sitagliptin do not increase the overall risk of CV events, pancreatitis or pancreatic cancer, but the risk of heart failure may be increased with saxagliptin (139–142) (see Treatment of Diabetes in People with Heart Failure chapter, p. S196).

The efficacy of the glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide, lixisenatide and dulaglutide) with respect to blood glucose, A1C and weight reduction is independent of age. These agents are well tolerated in the elderly with a similar side effect profile to younger people with diabetes, although there may be a higher risk of gastrointestinal side effects. There is a low risk of hypoglycemia when used as monotherapy or with metformin (143–148). Lixisenatide is not associated with an increase in CV events in elderly people who have recently had a similar event (149), and liraglutide and semaglutide improve CV outcomes in older people with diabetes and pre-existing cardiovascular disease (CVD) (150,151) (see Pharmacologic Glycemic Management of Type 2 Diabetes chapter, p. S88).

Colesevelam is generally well tolerated in the older person with diabetes and has a modest impact on A1C and lipid values (152).

Recently, data have become available on the use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin. empagliflozin and dapagliflozin) in the older person (153–160), although the numbers of participants over 70 years of age in these studies is not nearly as large as those with DPP-4 inhibitors. The studies have been done on participants without complex comorbidities, so it is not clear what the outcomes would be in less robust older people. These drugs are often contraindicated in the older adult due to reductions in glomerular filtration rate (GFR). They appear slightly less effective in terms of reductions in A1C in the older adult, likely because of lower GFRs in this age group. Although information is limited, the older person with diabetes may be more susceptible to dehydration and fractures than younger people treated with these agents, suggesting that they should be used cautiously. There does not appear to be an increased risk of bladder or skin infections, relative to younger patient populations. There have been no head-to-head studies of these drugs in comparison to DPP-4 inhibitors, specifically in the older person with diabetes. In a recent study of empagliflozin in participants with established CVD, the positive impact on CV outcomes was greater in those over, rather than under the age of 65 years, and the impact on renal outcomes was similar in both age groups (158,161). Canagliflozin also appears to have a greater impact on CV outcomes in people over age 65, but the increased risk of amputation and fractures give cause for concern (162). If subsequent studies confirm this finding and establish the safety of these compounds, they may be used more widely in the older age group. Because there is a much larger body of evidence with DPP-4 inhibitors to date in this age group, they should generally be used before SGLT2 inhibitors. Currently, empagliflozin could be considered for people <75 years with evidence of CVD, relatively preserved renal function and no other complex comorbidities.

Insulin therapy

Insulin regimens in the older adult should be individualized and selected to promote patient safety. Insulin absorption is similar from the arm and abdomen, and a skin lift is not required to optimize absorption (163). The abdomen is the preferred site for self-injection because it is easier for the older person to landmark. The clock drawing test and other cognitive assessments can be used to predict which elderly people are likely to have problems with insulin therapy (164,165). In older people, the use of prefilled insulin pens as an alternative to conventional syringes (166,167) minimizes dose errors and may improve glycemic control.

Pre-mixed insulin analogues can be administered after meals (168–170) and result in better and more durable control than basal insulins alone (171), but at the expense of more hypoglycemia and greater weight gain (172,173). When compared to premixed insulin, the combination of detemir and repaglinide results in equivalent glycemic control, with less weight gain, hypoglycemia and glycemic variability (174).

Basal-bolus injection regimens may be associated with greater improvements in glycemic control, health status and mood than twice-daily injections of long-acting insulin (175), although premixed insulin analogues can result in equivalent glycemic control to basal-bolus regimens (176). The addition of glargine to noninsulin antihyperglycemic agents results in improved control and a reduced frequency of hypoglycemia when compared to escalation of non-insulin antihyperglycemic agents (177). Both detemir insulin and glargine insulin U-100 have similar effectiveness in young and older people and result in a reduced rate of hypoglycemia when compared to 30/70 insulin or neutral protamine Hagedorn (NPH) (178–182). Glargine insulin U-300 is associated with a lower frequency of hypoglycemia than glargine U-100 in the older person (183). The kinetics of insulin degludec are similar in young and old people with diabetes (184). Older people appear to have less nocturnal hypoglycemia with insulin degludec than glargine U-100 (185).

Recently, it has been demonstrated that simplification of the insulin regimen in older people with type 2 diabetes by switching

multiple-dose insulin regimens to once-a-day glargine U-100 with or without noninsulin antihyperglycemic agents results in equivalent glycemic control and a reduced risk of hypoglycemia (186). This strategy should be more broadly applied in older people with multiple comorbidities and/or frailty.

In the future, older adults may be using newer technology for insulin administration. A randomized controlled trial of basal-bolus injection therapy vs. continuous subcutaneous insulin infusion (CSII) therapy in older people with type 2 diabetes found no difference in glycemic variability, treatment satisfaction, rates of hypoglycemia or glycemic control (187,188). People with type 1 diabetes <75 years of age who are highly functional have improved glycemic control and reduced symptomatic hypoglycemia using CSII (189–191). The ability to use more advanced pump features and the basal/bolus ratio appears to be similar in younger and older people (191). There is no data as yet favouring one pump device over another.

Finally, older people with diabetes are at increased risk for falls and fractures, and insulin therapy and sulfonylureas increase this risk (192,193).

Prevention and Treatment of Complications

Hypertension

Treatment of isolated systolic hypertension or combined systolic and diastolic hypertension in older people with diabetes is associated with a significant reduction in CV morbidity and mortality and microvascular events. The number needed to treat (NNT) reduces with increasing age (194–198). Treatment of isolated systolic hypertension may also preserve renal function in older people with diabetes (199). Several different classes of antihypertensive agents have been shown to be effective in reducing the risk of CV events and end stage renal disease (ESRD), including thiazide-like diuretics, long-acting calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) (194–204). Any of these agents is a reasonable first choice (200–202). Although the calcium channel blocker amlodipine may be associated with an increased risk of congestive heart failure (CHF) (202), the combination of ACE inhibitor and amlodipine appears to reduce CV events more than the combination of an ACE inhibitor and hydrochlorothiazide (205). Cardioselective beta blockers and alpha-adrenergic blockers are less likely to reduce CV risk than the above agents (200–203). ACE inhibitors may be particularly valuable for people with diabetes and >1 other CV risk factor (206).

In the ACCORD study, more intensive control of blood pressure (BP) (systolic BP <140 mmHg vs. <120 mmHg) in participants with type 2 diabetes at high risk for CV events, did not improve CV outcomes and resulted in more side effects (207). In older people with diabetes, systolic BP <130 mmHg and diastolic BP <67 mmHg may predict an increased mortality rate (36,208). As a result, there has been discussion about altering the systolic BP target for the elderly to 140 mmHg; however, Hypertension Canada in collaboration with Diabetes Canada have maintained the target BP <130/80 mmHg in diabetes (see Treatment of Hypertension chapter, p. S186), although this should be modified for people with diabetes with multiple comorbidities and limited life expectancy. The current guidelines from other international organizations and Diabetes Canada are shown in Table 2. There has been significant improvement in the number of older people treated for hypertension, and therapies being used are more consistent with current clinical practice guidelines (209).

Dyslipidemia

The treatment of dyslipidemia with statins for both primary and secondary prevention of CV events has been shown in most, although not all, studies to significantly reduce CV morbidity and mortality in older people with diabetes (210–218). In people with diabetes with limited life expectancy, consideration should be given to stopping or not starting these medications, as these people are unlikely to receive benefit. Current guidelines from other international organizations are shown in Table 2. The data on the use of fibrates in this patient population are equivocal (219,220), although they may reduce albuminuria and slow GFR rate loss (221).

Erectile dysfunction

Type 5 phosphodiesterase (PDE) inhibitors appear to be effective for the treatment of erectile dysfunction in carefully selected older people with diabetes (222–224). (See Sexual Dysfunction and Hypogandism in Men with Diabetes chapter, p.S228.)

Depression

Depression is common in older people with diabetes, and a systematic approach to the treatment of this illness not only improves quality of life, but reduces mortality (225). While screening for depression is not recommended, maintaining a high index of suspicion is advisable.

Osteoporosis

Type 1 diabetes is associated with low bone density although the mechanism of bone loss is unknown. The Nord-Trondelag Health Survey from Norway showed a significant increase in hip fracture rates among females with type 1 diabetes compared to females without diabetes (relative risk [RR] 6.9, 95% confidence interval [CI] 2.2–21.6) (226). In the Iowa Women's Health Study, women with type 1 diabetes were 12.25 times more likely to report having had a fracture compared to women without diabetes (227). The relationship between type 2 diabetes and osteoporosis is less clear. In some studies, people with type 2 diabetes had a higher bone mineral density than control populations (228,229); however, other studies have not found significant differences (230,231).

Dementia

Diabetes increases the risk of dementia in older people with diabetes, including both vascular dementia and Alzheimer's disease (62,232,233). This risk appears to be increased in women treated with unopposed estrogen therapy (233). As yet, there is no clear evidence that any particular intervention (i.e. healthy behaviour interventions, treatment of risk factors, etc.) will prevent dementia in this cohort.

Polypharmacy

Older people with diabetes are frequently on multiple medications, many of which may be inappropriate in the setting of complex comorbidity and limited life expectancy (234). In selected populations, deprescribing should be considered to reduce complexity of therapy, side effects and adverse drug interactions (235). Drugs that can be considered first for deprescribing in these individuals include statins and sulfonylureas, because of lack of benefit in people with limited life expectancy and concerns about hypoglycemia, respectively.

Diabetes in Long-Term Care

The prevalence of diabetes is high in institutions and individuals frequently have established microvascular and CV complications,

as well as substantial comorbidity (236–240). Canadian data shows over 25% of residents in long-term care facilities (LTC) have type 2 diabetes (241). Although the number of residents living in LTC with type 1 diabetes is unknown, a growing prevalence is noted as a result of advances of glucose management and adults being diagnosed with type 1 diabetes later in life, which requires the implementation of protocols specific for type 1 diabetes management (242). In observational studies, the degree of glycemic control varies widely between different centres (238,243), adherence to clinical practice guidelines is poor and insulin sliding scales (correction insulin only) are used frequently despite lack of evidence for their effectiveness (236,244). The complexity of antihyperglycemic medications is greater in LTC facilities than community-dwelling populations with most common patterns of therapy including insulin (245). Major problems faced by people with diabetes in LTC include: undernutrition (236), overly aggressive glycemic control with A1C levels below recommended target (<7.0%) (246) and polypharmacy. It has been shown that tight glycemic control with A1C <6.0% is associated with higher mortality in the aging population (35,36).

There are very few intervention studies on diabetes in LTC. The short-term substitution of a regular diet or a standard nutritional formula instead of a diabetic nutritional formula or "diabetic diet" did not modify the level of glycemic control (236,247–249). Available data about insulin therapy in people with diabetes in LTC settings are very scarce and great treatment variability of this population seems to prevail in current clinical practice (250). Substitution of regular insulin by lispro insulin at meal time may improve glycemic control with reduced number of hypoglycemic episodes in LTC patients (251). In a prospective randomized clinical trial in LTC, similar glycemic control was achieved with either basal insulin or with noninsulin antihyperglycemic agents in people with type 2 diabetes with no difference in the frequency of hypoglycemia, need for emergency room visits, hospital admission or mortality between treatment groups (252). The utilization of sliding scale insulin is prevalent in LTC and is associated with poorer glycemic control and higher frequency of capillary blood glucose (CBG) monitoring and hypoglycemia (244,250).

Frail older residents of LTC remain at high risk of hypoglycemia due to their advanced age, multiple comorbidities, polypharmacy, hypoglycemia unawareness and impaired renal function. To reduce risk of hypoglycemia, all antihyperglycemic agents have to be adjusted based on renal function (see Appendix 7. Therapeutic Considerations for Renal Impairment) at frequent intervals and higher glycemic targets are recommended for this high-risk population (see above). Deprescribing antihyperglycemic and other agents in high-risk people is recommended to achieve appropriate targets and reduce side effects of medication (235). Appropriate discontinuation of antihyperglycemic medication in older people who have tight glycemic control can potentially reduce risk of hypoglycemia and medication burden (253). Management of diabetes in LTC can be challenging as it requires an interprofessional team approach, collaboration with facility management, development of care protocols and acceptance of set treatment goals by the entire interprofessional team (254).

RECOMMENDATIONS

1. Functionally independent older people with diabetes who have a life expectancy of greater than 10 years should be treated to achieve the same glycemic, BP and lipid targets as younger people with diabetes [Grade D, Consensus].

2. BP targets should be individualized for older adults who are functionally dependent, or who have orthostasis, or who have a limited life expectancy [Grade D, Consensus].

3. In the older person with diabetes and multiple comorbidities and/or frailty, strategies should be used to strictly prevent hypoglycemia, which include the choice of antihyperglycemic therapy and less stringent A1C target [Grade D, Consensus]. Antihyperglycemic agents that increase the risk of hypoglycemia or have other side effects should be discontinued in these people [Grade C, Level 3 (235,253)].

4. A higher A1C target may be considered in older people with diabetes taking antihyperglycemic agent(s) with risk of hypoglycemia, with any of the following: [Grade D, Consensus for all]
   a. Functionally dependent: 7.1–8.0%
   b. Frail and/or with dementia: 7.1–8.5%
   c. End of life: A1C measurement not recommended. Avoid symptomatic hyperglycemia and any hypoglycemia.

5. The clock drawing test may be used to predict which older individuals will have difficulty learning to inject insulin [Grade C, Level 3 (164)].

6. Older people who are able should receive diabetes education with an emphasis on tailored care and psychological support [Grade A, Level 1A (24)].

7. If not contraindicated, older people with type 2 diabetes should perform aerobic exercise and/or resistance training to improve glycemic control as well as maintain functional status and reduce the risk of frailty [Grade B, Level 2 (73–77)].

8. In older people with type 2 diabetes, sulphonylureas should be used with caution because the risk of hypoglycemia increases substantially with age [Grade D, Level 4 (108)].
   a. DPP-4 inhibitors should be used over sulfonylureas as second-line therapy to metformin because of a lower risk of hypoglycemia [Grade B, Level 2 (137)]
   b. In general, initial doses of sulphonylureas in the older person should be half of those used for younger people, and doses should be increased more slowly [Grade D, Consensus]
   c. Gliclazide and gliclazide MR [Grade B, Level 2 (113,115,119)] and glimepiride [Grade C, Level 3 (114)] should be used instead of glyburide, as they are associated with a reduced frequency of hypoglycemic events
   d. Meglitinides may be used instead of glyburide to reduce the risk of hypoglycemia [Grade C, Level 2 (121) for repaglinide; Grade C, Level 3 (122) for nateglinide], particularly in individuals with irregular eating habits [Grade D, Consensus].

9. In older people with type 2 diabetes with no other complex comorbidities but with clinical CVD and in whom glycemic targets are not achieved with existing antihyperglycemic medication(s) and with an eGFR >30 mL/min/1.73 m^2, an antihyperglycemic agent with demonstrated CV outcome benefit could be added to reduce the risk of major CV events [Grade A, Level 1A (161) for empagliflozin; Grade A, Level 1A (150) for liraglutide; Grade C, Level 2 (162) for canagliflozin].

10. Detemir, glargine U-100 and U-300 and degludec may be used instead of NPH or human 30/70 insulin to lower the frequency of hypoglycemic events [Grade B, Level 2 (181) for glargine U-100; Grade B, Level 2 (182) for detemir; Grade D, Consensus for degludec and glargine U-300].

11. In older people, premixed insulins and prefilled insulin pens should be used to reduce dosing errors and to potentially improve glycemic control [Grade B, Level 2 (166,167)].

12. In older LTC residents, regular diets may be used instead of "diabetic diets" or nutritional formulas [Grade D, Level 4 (247–249)].

13. Sliding scale (reactive) and correction (supplemental) insulin protocols should be avoided in elderly LTC residents with diabetes to prevent worsening glycemic control [Grade C, Level 3 (244,250)].

Abbreviations:
A1C, glycated hemoglobin; *ACE*, angiotensin-converting enzyme; *ARC*, angiotensin receptor blocker; *BP*, blood pressure; *CBG*, capillary blood glucose; *CGM*, continuous glucose monitoring; *CHF*, congestive heart failure; *CSII;* continuous subcutaneous insulin infusion; *CV*, cardiovascular; *CVD*, cardiovascular disease; *DHC*, diabetes health care; *DPP-4*, dipeptidyl peptidase-4; *ESRD*, end stage renal disease; *GFR*, glomerular filtration rate; *GLP*, glucagon-like peptide; *HDL-C*, high-density lipoprotein cholesterol; *LTC*, long-term care; *MI*, myocardial infarct; *NPH*, neutral protamine Hagedorn; *SGLT*, sodium glucose co-transporter; *SMBG*, self-monitoring of blood glucose; *TZD*, thiazolidinedione.

Other Relevant Guidelines

Screening for Diabetes in Adults, p. S16
Reducing the Risk of Developing Diabetes, p. S20
Organization of Diabetes Care, p. S27
Self-Management Education and Support, p. S36
Targets for Glycemic Control, p. S42
Glycemic Management in Adults With Type 1 Diabetes, p. S80
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Hypoglycemia, p. S104
Screening for the Presence of Cardiovascular Disease, p. S170
Dyslipidemia, p. S178
Treatment of Hypertension, p. S186
Sexual Dysfunction and Hypogonadism in Men With Diabetes, p. S228

Relevant Appendix

Appendix 7. Therapeutic Considerations for Renal Impairment

Author Disclosures

Dr. Meneilly reports personal fees from Merck, Novo Nordisk, and grants from Sanofi, outside the submitted work. Dr. Miller reports personal fees from AstraZeneca, Eli Lilly, Novo Nordisk, and Sanofi; grants and personal fees from Boehringer Ingelheim, Janssen, and Merck, outside the submitted work. Dr. Sherifali reports investigator-initiated funding from AstraZeneca. Dr. Tessier has received honoraria from Merck, AstraZeneca, Boehringer Ingelheim, and Elli Lilly. Dr. Zahedi has received honorarium for CME programs and Advisory Boards from the following companies: Eli Lilly, Merck, Novo Nordisk, and Sanofi. No other authors have anything to disclose.

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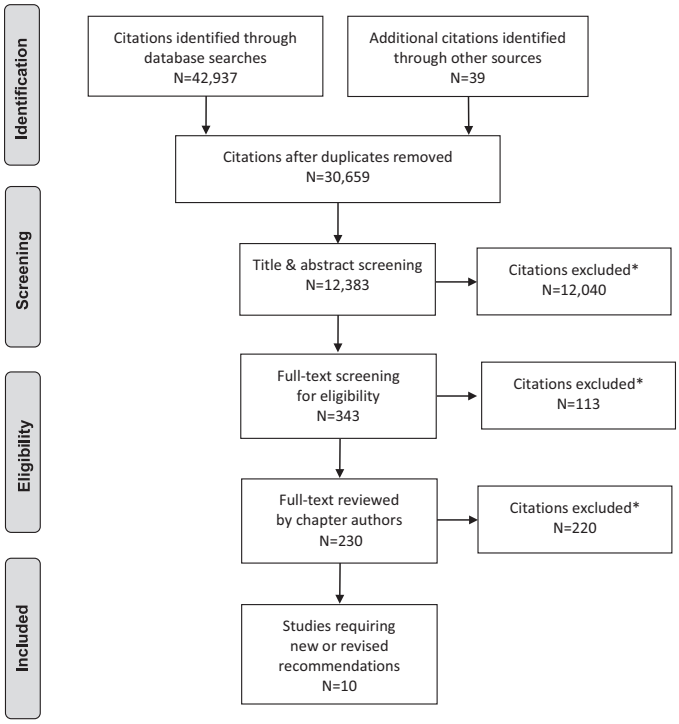
Literature Review Flow Diagram for Chapter 37: Diabetes in Older People



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (255).

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2018 Clinical Practice Guidelines

Type 2 Diabetes and Indigenous Peoples

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- Indigenous peoples living in Canada are among the highest-risk populations for diabetes and related complications. Screening for diabetes should be carried out earlier and at more frequent intervals.
- Effective prevention strategies are essential and should be grounded in the specific social, cultural and health service contexts of the community. Prediabetes is an important opportunity to prevent or delay diabetes with healthy behaviour interventions and/or metformin.
- Particular attention is needed for Indigenous women and girls of childbearing age, as the high incidence of hyperglycemia in pregnancy (gestational and type 2) and maternal obesity increases the risk of childhood obesity and diabetes in the next generation. Early identification of diabetes in pregnancy is important, and postpartum screening for diabetes in women with a history of gestational diabetes should be performed along with appropriate follow up.
- Diabetes management targets in Indigenous peoples should be no different from the general population. A focus on building a therapeutic relationship with an Indigenous person with diabetes is important rather than a singular emphasis on achieving management targets. The current poor success at achieving management targets highlights the limitations of health services when they are not relevant to the social and cultural contexts of Indigenous peoples.
- A purposeful process of learning and continuous self-reflection is required by the health-care worker to integrate Indigenous-specific contexts within the clinical approach to diabetes management.

KEY MESSAGES ABOUT DIABETES FOR INDIGENOUS PEOPLES AND THEIR COMMUNITIES

- Many Indigenous communities have families with high rates and high risk of type 2 diabetes. If you are in a community with high rates of diabetes, see a health-care provider to learn about ways to be tested for and prevent diabetes.
- The causes of diabetes are complex. Learning about the medical, social and cultural contributions to diabetes is key to diabetes prevention. In particular, seek to understand the relationships between the history of colonization and the current high rates of diabetes in Indigenous peoples.
- Ask about community initiatives that promote healthy behaviours, such as diabetes walks, weight-loss groups, fitness classes, community kitchens and gardens, and school-based activities for children and teenagers.
- If you are planning a pregnancy or may get pregnant, get screened for diabetes. If you are pregnant and have diabetes or have been diagnosed with gestational diabetes, visit your health-care providers more often, and find out about exercise, breastfeeding and other support groups for pregnant women and new mothers.

PRACTICAL TIPS FOR HEALTH-CARE PROVIDERS CARING FOR INDIGENOUS PEOPLES

- Acknowledge the legacy of colonization and its ongoing adverse effects on Indigenous health. This legacy:
  - Maintains socioeconomic disadvantage that limits healthy choices (diet, physical activity, adherence to medication, etc.), increases levels of stress, and decreases capacity for self-care and healthy behaviour change;
  - Perpetuates a toxic social environment for the individual, family, and community with pervasive and accumulated psychosocial adversities throughout the life-course;
  - Stirs experiences of shame and stigma with a diagnosis of diabetes;
  - May recall residential school-like conditions with health-care provider expectations that Indigenous peoples with diabetes will acquire diabetes knowledge and produce “test” results.
- In clinical interactions, recognize, explore and acknowledge:
  - Discord within the therapeutic relationship that may arise from heightened apprehension by the Indigenous person with diabetes as well as emotional reaction to prejudice, power and authority asserted by health-care providers;
  - Interconnectedness between socioeconomic disadvantage, adverse life experiences and capacity for managing diabetes;
  - One’s own (i.e. the health-care provider’s) concepts of health, diabetes care and assumptions about Indigenous perspectives;
  - The Indigenous person’s preferences and barriers for re-connecting and integrating cultural resources and traditional approaches to care.
- Engage and connect broadly with the Indigenous community to:
  - Implement prevention efforts and screening, with special attention to children and pre-gestational women, as well as the building of culturally safe interprofessional teams, diabetes registries and surveillance systems;
  - Foster positive relationships at the individual, family and community levels that advocate for family and community resources for Indigenous peoples;
  - Include traditional and cultural leadership to learn about local beliefs, practices and healing resources.

Note: In this document, the terms Aboriginal and Indigenous are generally used interchangeably. Indigenous peoples is the term accepted by the United Nations Declaration on the Rights of Indigenous Peoples, and is in increasing usage today. In the Canadian context, there are 3 Aboriginal groups recognized by the Constitution: First Nations, Inuit and Métis. It is important to recognize that while many Indigenous peoples live in their original land-based communities, which are mostly rural or remote, as many as 50% live in cities and towns, and may or may not choose to self-identify. Furthermore, wherever they live, Indigenous peoples’ customs can vary greatly, according to band or group affiliation, religion, education or a variety of other factors.

Conflict of interest statements can be found on page S303.

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Introduction

Improving health outcomes for Indigenous peoples with diabetes requires sufficient capacity and quality of health-care resources that are grounded in the person's specific social and cultural needs and contexts. Diabetes within the Indigenous population is complex and socially mediated (1,2). In 1 study, Indigenous peoples with diabetes perceived physicians as having limited awareness of the social factors affecting health (3). In contrast, physicians identified individual and systems barriers to exploring these issues. Elucidating the vital relational and culturally informed aspects of care that might enable the facilitation of improved diabetes outcomes requires focusing on culture as a resource. As connection to a traditional world view and way of life can be protective, it is important for health-care providers to be able to appropriately elicit and support Indigenous peoples with diabetes who may want to (re)engage in cultural practices (4,5).

In order to redress the legacy of residential schools and related colonial policies, and to advance the process of reconciliation in Canada, in 2015 the Truth and Reconciliation Commission (TRC) made 94 calls to action related to many domains of public life, including health (6). Within the calls to action, the TRC outlined a health service role in reconciliation through fostering health-care quality and equity specific to the needs of Indigenous peoples and communities. In order to realize that role, the TRC identified that health-care providers must understand how colonization has resulted in the current health status of Indigenous peoples. TRC call number 18 emphasizes that health systems be responsive and mobilize resources to address the distinct needs of Indigenous peoples, calling upon:

> *". . .federal, provincial, territorial, and Aboriginal governments to acknowledge that the current state of Aboriginal health in Canada is a direct result of previous Canadian government policies, including residential schools, and to recognize and implement the health-care rights of Aboriginal people as identified in international law, constitutional law, and under the Treaties"* (6).

Indigenous peoples around the globe are disproportionately affected by diabetes (7,8) and related complications. In Canada, age-standardized prevalence rates for diabetes are 17.2% among First Nations individuals living on-reserve, 10.3% among First Nations individuals living off-reserve, and 7.3% among Métis people, compared to 5.0% in the general population (9). A recent study in Alberta suggested that the lifetime risk of diabetes was 8 in 10 for First Nations persons over the age of 18 years compared with 5 in 10 for non-First Nations people (10). Among the Inuit people, the age-standardized prevalence rate of diabetes is comparable to that seen in the general Canadian population, but there is concern that rates will rise with large-scale changes impacting healthy behaviour in the far North (11).

Indigenous individuals are diagnosed at an increasingly younger age (12), have greater severity at diagnosis, develop higher rates of complications (13–15), and experience poorer treatment outcomes. The rising incidence among youth and young adults (12,16,17) has been shown to be accompanied by 2.6 times higher rates of end-stage renal disease (ESRD) and death in First Nations compared to non-First Nations persons diagnosed under 20 years of age (18). Higher prevalence rates of microvascular disease, including chronic kidney disease (CKD) (19), lower limb amputation (20,21), foot abnormalities (22,23), and more severe retinopathy (24) have been found. Indigenous peoples are also burdened by higher rates of cardiovascular disease (CVD) (20,25) and exhibit higher rates of cardiometabolic risk factors, including smoking, obesity and hypertension (19,20,26).

In contrast to the general population, a disproportionate burden of diabetes affects First Nations women (27,28), and may be related to an increased prevalence of diabetes complicating pregnancy (27,29,30), as well as poorer documented health outcomes (30,31) and a more rapid progression to type 2 diabetes (32,33). A recent Australian review reported a greater prevalence of gestational diabetes mellitus (GDM) in Indigenous women, as well as increased rates of adverse outcomes of diabetes in pregnancy, including macrosomia, caesarean section, congenital deformities, low birth weight, hypoglycemia and neonatal trauma (34). These adverse outcomes were greater in rural/remote populations.

Diabetes in Indigenous populations globally is linked to a complex array of factors; however, a common thread is the shared history of colonization (35). The World Health Organization has recognized colonization as the most significant social determinant of health affecting Indigenous peoples worldwide (35). In Canada, this involved: the outlawing of Indigenous gatherings and ceremonies at the end of the nineteenth and throughout the first half of the twentieth centuries; forced community relocations; mandatory residential school attendance where Indigenous languages were forbidden and physical and sexual abuse were common; and discriminatory child welfare legislation that persists today (36). All have undermined Indigenous cultures and values, leading to lasting and intergenerational effects on mental health, family relationships and Indigenous ways of knowing and connecting to the land (37,38). Similar actions were common during the "settlements" of Australia, New Zealand and the United States, with ongoing parallels in chronic disease statistics. It is also essential to realize that the impacts of colonization continue through persisting inequities, exclusion and oppression of Indigenous peoples within Canada.

Other factors contributing to the incidence gap faced by Indigenous peoples include the probable influence of diabetes in pregnancy and the intrauterine milieu (39). Also postulated are possible environmental exposures, such as mercury (40), arsenic (41), polychlorinated biphenyl (PCB) and chlorinated pesticide exposure (42,43). Low levels of vitamin D have also been implicated (44). In addition, genetic vulnerability has been shown to be relevant (45–48), and markers have been studied in Pima Indians in Arizona (49), and are known in the Canadian Ojibway Cree population (50,51). In the Inuit, the TCB1G4 gene leads to a specific kind of type 2 diabetes with abnormal postprandial glucose and normal glycated hemoglobin (A1C); however, there are unclear implications for the role of genetic testing in clinical practice (52).

There is emerging literature on the effect of adverse childhood experiences and subsequent incidence of type 2 diabetes (53,54). In the Indigenous context, stress is accumulative and arises from multiple psychosocial sources (55–58). Poverty is a common experience, which hinders access to needed resources (e.g. healthy foods), as are direct/indirect traumatic experiences resulting from residential schools and child welfare systems (e.g. unresolved grief) (59,60). When stressors operate concurrently, along with living conditions that are overwhelming or chaotic, one's capacity to cope and manage diabetes is undermined. Whether linked to stress or poor dietary patterns, obesity is the most common proximal determinant of diabetes (11,61). One study found "beef and processed foods" to be associated with incident diabetes, whereas "balanced market foods" and "traditional foods" were not predictive, after adjustment for confounders, including waist circumference and adiponectin (62).

The increasing burden of diabetes in Indigenous populations is a major and growing challenge for health systems and Indigenous communities alike, whether First Nations, Inuit or Métis (63). Processes of care have been found to be deficient in 2 large studies in Alberta, associated with greater morbidity and mortality (17,64). A national survey found serious health service challenges for Indigenous populations (65); and a recent review corroborated the survey and suggested there was no best practice evidence out of 17 reviewed Canadian publications between 2008 and 2014

(66). Improving health outcomes would involve ensuring health service quality and equity tailored to the needs of Indigenous peoples with diabetes. This means addressing the social origins of disease and illness located within Indigenous contexts of colonization, inequity and exclusion. New approaches to care are needed that are culturally congruent with Indigenous perspectives and grounded in addressing the impacts of colonization on health that Indigenous peoples continue to experience.

Screening in Indigenous Peoples and/or Communities

Screening and prevention strategies should be implemented in collaboration with community leaders, Indigenous peoples with diabetes, health-care professionals, and funding agencies to engage entire communities, promote environmental changes and prevent increased risk of diabetes in all Indigenous populations, not just rural or remote (67). Such partnerships are important for prioritizing and incorporating local social and cultural contexts, building both trusting relationships and community capacity, enhancing diabetes-related knowledge, and increasing the likelihood of success and sustainment of prevention efforts.

Screening for diabetes in asymptomatic Indigenous adults (>age 18 years) should be considered every 6 to 12 months in those with additional risk factors, especially those with overweight or obesity, those with strong family histories, or women of childbearing age (see Screening for Diabetes in Adults chapter, p. S16), ensuring facilitation of access to clinical care, such that testing can lead to significant follow up action. Regular screening and follow-up is also encouraged in individuals with prediabetes [impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)], history of GDM, or polycystic ovary syndrome (PCOS), as 20% to 50% of high-risk individuals with IFG may have a 2-hour plasma glucose (PG) ≥11.1 mmol/L (68).

Screening recommendations for Indigenous children and adolescents are outlined in the Type 2 Diabetes in Children and Adolescents chapter, p. S247. As Indigenous children already possess 1 risk factor (high-risk ethnic group), screening for type 2 diabetes should be considered every 2 years, using a combination of an A1C and a fasting plasma glucose (FPG) if they possess ≥2 additional risk factors in non-pubertal children beginning at 8 years of age or ≥1 additional risk factor in pubertal children. Risk factors include obesity; first-degree relative with type 2 diabetes and/or exposure to hyperglycemia in utero, or if they have signs and symptoms of insulin resistance, prediabetes, or use atypical antipsychotic medications (see Recommendation 3. Type 2 Diabetes in Children and Adolescents chapter, p. S251).

Screening has proved possible in both rural and remote communities through appropriate dialogue, respect and planning; with the provision of concomitant health education and care; and the promotion of follow up (26,69–72). In Alberta, substantial numbers of Indigenous individuals with abnormalities have been identified through community-based screening with point-of-care (POC) instruments handled by trained health-care professionals and associated with a quality control program (72). POC A1C screening has shown to be sufficiently accurate as a screening tool for diagnosing diabetes in remote communities (73,74); however, currently, no POC A1C analyzers are approved for the diagnosis of diabetes in Canada (see Monitoring Glycemic Control chapter, p. S47).

While screening with reflectance capillary blood glucose meters is not recommended, it should be noted that it has often happened and continues to happen in community contexts. It is essential that this type of screening be confirmed in a health-care setting. When Indigenous peoples with diabetes are educated on the use of reflectance capillary blood glucose meters, these cautions should be discussed, and infectious disease precautions emphasized.

Retinal photography screening has also been utilized in Canada in remote areas (75), and has been shown to increase the number of screened individuals in Australia (76) (see Retinopathy chapter, p. S210). In the United States, a kidney evaluation program screened 89,552 participants in 49 states, 4.5% of whom were Native American (71).

Depression is associated with type 2 diabetes (77), for which screening and treatment should follow existing best practices. While individuals may benefit from the diagnosis and treatment of depression and other mental health illnesses, cultural approaches may be more appropriate (4,5). Furthermore, several studies have demonstrated associations between greater cultural continuity and better mental health outcomes. Local traditional approaches to wellness around management and support for depression should be explored when appropriate.

Pregnant Indigenous women identified as being at high risk for type 2 diabetes based on clinical risk assessment should be screened with an A1C test at the first antenatal visit to identify pre-existing diabetes (78). For those women with a hemoglobinopathy or renal disease, the A1C test may not be reliable and screening should be performed with an FPG (see Monitoring Glycemic Control chapter, p. S47). If the A1C is ≥6.5% or the FPG is ≥7.0 mmol/L, the woman should be considered to have diabetes in pregnancy and SMBG should start, along with nutritional counselling (see Diabetes and Pregnancy chapter, p. S255). While there is insufficient data on the best tests and their diagnostic interpretation in the early trimester for lower levels of abnormal glycemia, e.g. A1C between 5.7% and 6.4% or FBG between 5.1 and 6.9 mmol/L (see Diabetes and Pregnancy chapter, p. S255), the rationale for screening remains strong, particularly to detect previously undiagnosed type 2 diabetes. However, further research is needed as a recent systematic review pointed out the insufficient evidence regarding cost effectiveness of early testing, as well as information on longer-term benefits (79). If the initial screening is performed before 24 weeks of gestation and is negative, the woman should be re-screened for GDM between 24 to 28 weeks of gestation (see Diabetes and Pregnancy chapter, p. S255). In addition, all women not previously screened for diabetes should be tested between 24 to 28 weeks of gestation.

Postpartum screening after GDM should be carried out between 6 weeks and 6 months, and accompanied with healthy behaviour interventions and ongoing monitoring or treatment (see Diabetes and Pregnancy chapter, p. S255). To date, rates of postpartum OGTT screening have been shown to be low, indicating that new approaches may be required to account for challenges among women with a new baby to find time to do screening tests, let alone capacity to do so while breastfeeding. Such challenges support the case for A1C and random or fasting glucose, POC testing, and messages that emphasize the benefit of delaying disease onset rather than diagnosing a condition that may be felt by affected women to be "expected and assumed" (80,81).

Primary Prevention

Prevention of type 2 diabetes in those with identified prediabetes (IGT/ IFG) is now an established desired practice (82,83). Proven interventions include healthy behaviour changes and regular physical activity that induce moderate weight loss. Metformin may also be used (see Reducing the Risk of Developing Diabetes chapter, p. S20). The Diabetes Prevention Program from the United States was effective for all ethnicities, but the extent to which it can be applied in Canadian Indigenous contexts is unknown. Primary prevention approaches within Indigenous communities have been undertaken in Canada by the Aboriginal Diabetes Initiative (ADI) (84) and have focused on common risk factors, including obesity, sedentary lifestyle and unhealthy diet, as well as through

interventions aimed at increasing health literacy and access to physical activity. Community involvement in developing the intervention and framing the intervention within Indigenous cultural perspectives have been variable. Results of the ADI are unknown. A study with Algonquin women sought to understand the cultural factors that would likely impact the prevention of diabetes, identifying the following factors: the importance of family and social ties; the possibility of preserving cultural values; the opportunity to learn behaviours through educational resources adapted to needs and culture; the possibility of saving money through better diet and access to self-monitoring of blood glucose (SMBG) supplies (85).

In Arizona, 95 men and women with obesity and normoglycemia between the ages of 25 to 54 years were randomized to treatments named "Pima Action" (Action) and "Pima Pride" (Pride) and followed for 12 months. "Action" involved structured activity and nutrition interventions; and "Pride" included unstructured activities, emphasizing Pima history and culture. Action members gained more weight and had higher BG levels at the end of the study, suggesting that less structured and more culturally-grounded interventions may be more relevant and successful (86). More recently, a prevention study in 3,135 participants in 36 Indigenous communities in the United States showed baseline psychosocial characteristics of family support and psychological distress predicted favourable baseline weight and weight change post-intervention, while coping skills and trauma exposure did not (87).

In light of the disproportionate burden of diabetes, appropriate population level prevention approaches are critical investments. Nevertheless, it remains unclear whether increased knowledge and awareness, or increased community physical activity resources fill a gap created by structural barriers from social inequities and colonization. Prevention should be critically informed by the social contexts that shape the health of Indigenous peoples, as well as resourced to ensure effectiveness and sustainability. For example, the United States-based Traditional Foods Project aimed to increase access to traditional foods, physical activity and social support (88). Indigenous communities across the country applied their traditional ecological knowledge, specific to the history and culture of their tribe, to protect their communities' land, languages, culture, memory and traditional food practices. Sharing and documenting food sovereignty was a priority. A collection of stories told by tribes about their traditional foods systems was published on the Native Diabetes Wellness Program website. Underpinning the stories are long-sighted lessons for sustainability, embedded in cultural significance and emotional attachment, and inspired by agency (i.e. capacity of acting or of exerting power), self-determination, and hope, for the health of the people (89).

Type 2 diabetes in Indigenous youth is the fastest growing pediatric chronic disease worldwide (16), with childhood obesity as the immediate determinant. The latest Cochrane review of prevention efforts with respect to childhood obesity indicated the following to be promising policies and strategies: school curriculum that includes healthy eating, physical activity and positive body image; increased sessions for physical activity and the development of fundamental movement skills throughout the school week; improvements in nutritional quality of the food supply in schools; environments and cultural practices that support healthy eating and physical activity throughout the day for children; teacher/staff support to implement health promotion strategies and activities (e.g. professional development, capacity-building activities); and parent support and home activities that encourage children to be more active, eat more nutritious foods, and spend less time in screen-based activities (90). While many of these measures have been applied in the Indigenous context, studies have been small, designs have been disparate and the degree of engagement with the community has been variable (91). Two prime examples in Canada were carried out in Kahnawake and Sandy Lake, where broad community-based participatory research projects were conducted (67,92). Although unpublished, "Drop the Pop" campaigns have taken hold in various communities. Similarly, the Traditional Foods Project's partners offered insight to the Bureau of Indian Education in the United States, as they developed their School Health and Wellness Policy supporting the provision for "healthy traditional and cultural foods". Tribal schools also are providing hands-on learning activities about growing healthy foods. Sustainability of these activities is strengthened by local and national efforts, including the "Farm to School" initiative (93).

In the United States, Zuni First Nations children who received an educational component targeting decreased consumption of sugared beverages, knowledge of diabetes risk factors, and access to a youth-oriented fitness centre demonstrated significantly decreased insulin resistance (94). These types of interventions aimed at decreasing childhood obesity, as well as efforts to promote breastfeeding in the first year of life (95), may help to reduce the risk for diabetes in Indigenous youth.

Finally, pregnancy provides an optimal window of opportunity for intervention to reduce long-term risk for both mothers and offspring. Strategies aimed at the prevention of pre-gravid obesity prior to first conception or subsequent pregnancy may be important tools to decrease the incidence of GDM (96) and type 2 diabetes in pregnancy, thereby potentially decreasing the incidence of diabetes in subsequent generations of Indigenous peoples (39).

Management

Similar to prevention strategies, management of diabetes with Indigenous peoples should incorporate the social and cultural contexts of the community from which the person originates, while also adhering to current clinical practice guidelines (66). One pilot study with a wait-list control group in Native Hawaiians showed that culturally adapted diabetes self-management education building on culturally relevant knowledge and activities (i.e. group-based educational format to facilitate social support, convenient community location, delivered by local community members in the local language, incorporation of local images/food/common physical activities/local people to increase relevance) for 3 months improved A1C, diabetes understanding and diabetes self-management (97,98). In a qualitative study in rural Australia, participants reported both negative influences (i.e. poor access to culturally appropriate health services, dislocation from cultural support systems, exposure to racism, poor communication with health-care professionals and economic hardship) and positive influences (i.e. cultural and traditional knowledge) that affected their health and well-being (99). Participants said that while they often felt overwhelmed and confused by the burden of chronic illness, they drew strength from being part of an Indigenous community, having regular and ongoing access to primary health care, and being well-connected to a supportive family network. Within this context, elders played an important role in increasing people's awareness of the impact of chronic illness on people and communities (99). Another qualitative study conducted with Canadian urban First Nations suggested they and their caregivers struggled with balancing two worlds, accessing care, and dealing with diabetes from cultural and emotional perspectives (100). A recent study of health-care experiences among Indigenous people with type 2 diabetes highlights the perpetuation of inequalities in care from a sample drawn from 5 Indigenous communities in 3 Canadian provinces (101). While service providers were identified as capable of mitigating potential for harm through engaging with patients' social worlds, a corresponding analysis of physician experiences of

providing care to Indigenous peoples with type 2 diabetes highlights structural barriers undermining capacity to shift clinical relationships (102). A recent analysis of a well-established program in Northern Québec showed that Indigenous peoples with diabetes had frequent contacts with the system, but gaps in the management of complications (103). Finally, a recent systematic review found that multiple system-level approaches are required in the delivery of health-care for diabetic foot disease in Indigenous peoples (104).

While most diabetes education programs work most effectively when delivered by interprofessional teams, in Indigenous communities, where access to physicians and other critical allied health professionals is often limited, strategies to improve care should focus on building capacity of existing health-care providers (e.g. community health-care providers, nurses to implement clinical practice guidelines) (26,105–107). A diabetes/chronic disease management program in a Hawaiian/Samoan Indigenous population successfully incorporated self-management and patient education to address nutrition and exercise, utilizing community health workers in the application of clinical practice guidelines. The study demonstrated a significant improvement in A1C levels and patient knowledge of reducing consumption of unhealthy foods (108). Maori and Pacific Islander adults with type 2 diabetes and CKD received community care provided by local health-care assistants to manage hypertension and demonstrated a reduction in systolic blood pressure (BP) and in 24-hour urine protein, and a greater number of prescribed antihypertensives; left ventricular mass and left atrial volume progressed in the usual care group, but not in the intervention group (109).

Regarding cost-effectiveness, a systematic review of primary care initiatives in Indigenous adult populations in Canada, Australia, New Zealand and the United States examined increased funding, system-level initiatives and single service components, concluding that the literature in this area was insufficient to make recommendations (110). Of 2,714 publications, only 13 met the authors' inclusion criteria (interventions aimed at improving the health system, clinic system or service level), and only 6 showed improvements in surrogate outcomes. The review highlighted the general reliance on intermediate health outcomes and observational studies, and stressed the need for larger, more rigorous studies with more robust outcomes of interest (i.e. hospitalizations, mortality) to support policy and practice recommendations (110).

Multifaceted clinical organizational and team-based interventions that have suggested benefit include: diabetes registries, recall systems, care plans and training for community health workers, and outreach services. Despite the effectiveness of multifaceted interventions, key elements are unclear (111–113) and the economic effectiveness is undetermined (114). Two newer Australian studies show that cycles of quality improvement that focus on organizational systems improve processes of care in pregnant women (115), as well as in-care processes and some surrogate outcomes in type 2 diabetes (116). Quality improvement processes with community-driven initiatives have demonstrated improvements in A1C testing from 41% to 72%, with an increase in the proportion of people at target A1C (<7.0%) from 19% to 28% (113). In Canada, provincial and federal government-led quality improvement projects have demonstrated improvements in type 2 diabetes outcomes in non-Indigenous settings (117–119). Indigenous-specific project funding is needed to examine the impact of community-driven quality improvement initiatives that are rooted in a cultural lens and prioritize community needs, resources and policies. Finally, management of diabetes in women in the child-bearing years should focus on the identification and optimal treatment of pre-existing (undiagnosed) diabetes as it is commonly missed and has been associated with poor outcomes, including an increased risk for stillbirth (30,120).

E4E VIGNETTE:

Dorothy is a 55-year-old female from a reserve adjacent to your rural practice. She has attended your clinic over the years for her general health needs and, most recently, for hypertension. She has booked to see you because she is concerned she has diabetes. Dorothy has a strong family history of diabetes and mentions that a close friend was recently quite ill and diagnosed as well. Dorothy has symptoms of diabetes, so you send her for bloodwork, confirming the diagnosis.

You call her back to the clinic to inform Dorothy of this diagnosis and the need for her to begin self-monitoring of her blood glucose in order to determine appropriate treatment. As expected, she is upset about the news but quickly settles, so you begin to provide your usual brief overview of diabetes, self-monitoring approach, and management tips. You summarize by encouraging her to eat well and exercise. She agrees to your offer of a referral for more diabetes education. You provide a prescription for a glucose meter and ask her to book an appointment with you in a few weeks.

Nine months later, Dorothy returns for a refill of her antihypertensive medications and to re-engage about the diagnosis of diabetes. You realize she did not follow up from her last visit, which is quite similar to your other Indigenous patients. You inquire, and Dorothy reveals that she was so upset and overwhelmed with the delivery of the diabetes diagnosis and your subsequent approach during the last visit, that she went into denial. You are surprised because you felt that the appointment went well and that your summary and plan were clear and concise.

For moving forward at this critical moment within the clinical interaction, aspects of the care framework are highlighted:

Dorothy indicated that she was upset and overwhelmed by you during the last visit. Pertinent to this discord, the care framework suggests that health-care providers "Become aware of and explore moments of discord, paying particular attention to patient resistance, hesitation and withdrawal, which possibly arise from tensions in historical relationships." You do so by asking about what upset and overwhelmed her about your approach. She hesitates but eventually explains that she feels as though you do not always care about her concerns, that you see her as taking up your precious time. She also adds that when you recommended she eat more vegetables, like carrots, it made her remember an experience in residential school, where a residential school worker once locked her in a cell in which all she had to eat for three days was a single carrot. She says that when she had tried to speak up, she felt you spoke over her, so was unable to communicate her anxieties. *The practice tips indicated above and E4E culture-based strategies in the table offer guidance for an enhanced health-care provider response.*

Because you acknowledged your role causing Dorothy to withdraw from the interaction, Dorothy seems more at ease and states she is ready to focus on addressing her diabetes. The care framework suggests that health-care providers explore social contexts that may influence diabetes, and so you enquire about social resource limitations in her life and adverse life experiences that may be factors. She asks why, and then explains that she is her grandchildren's primary caregiver, depended on by many people but without anyone to turn to for her own support. She also speaks about her fear of losing her job due to a hostile work environment in which even taking time off to visit the doctor is difficult. You share that those factors cause stress and are known in the research to diminish her resilience and often become barriers to health. The care framework recommends that acknowledging the impacts of these social factors and identifying patient priorities are important steps at this phase. You do so, naming concepts of effort-reward imbalance (123) and lateral violence (124). These resonate with her, and she asks for tips to address these in her life, to work on together with her diabetes.

Educating for Equity (E4E) Care Framework

Much of the above literature indicates that the context of traditions, language and culture could play an important role in the care physicians provide, since usual approaches have had limited effect. Emerging evidence from an international research team, *Educating for Equity* (121), indicates that diabetes management should more directly focus on social and cultural aspects specific to Indigenous populations. The E4E framework guides physicians in addressing social and cultural domains in their clinical interactions with patients. Core directives guide providers to: ensure reciprocal relationships, recognize the diversity of patients, provide care specific to each patient's needs, support them in developing capacity for addressing social determinants of health, and respect patient

Table 1
Educating for Equity (E4E) Clinical Strategies

E4E *Strategies for addressing social barriers to improve diabetes outcomes:*
Social & economic resource disparities • Screen for and explore resource limitations that influence diabetes onset and management • Acknowledge with the patient the impact of resource limitations on diabetes onset and management • Support access to key proximal health determinants • Assess diabetes knowledge and health literacy
Accumulation of adverse life experiences • Acknowledge with the patient connections between adverse life experiences and their capacity for diabetes management • Explore patient perspectives on personal adverse experiences in the context of diabetes in order to address their own priorities
Colonization, inequity and health care • Critically reflect on one's own stereotypes, assumptions and biases • Identify and explore moments of discord, paying particular attention to patient resistance, hesitation and withdrawal • Negotiate an agreeable power balance • Refrain from an authoritarian approach that relies on language rooted in oppression and racism
Educating for Equity *Strategies for facilitating outcomes using a cultural approach:*
Culture is therapeutic • Strive for cultural congruency of management recommendations • Explore patient preferences and support choices for accessing cultural resources • Engage with the community to learn of local beliefs and practices, and healing resources
Culture informs relationships • Reflect on professional distance and objectivity and, in the spirit of reciprocity, consider sharing about yourself to build trust • Adjust your pace when exploring the patient's world • Connect and work to foster positive relationships at the individual, family and community levels
Culture frames knowledge • Build a shared understanding of diabetes that integrates and contextualizes biomedical, social, political and cultural explanatory frameworks • Use language appropriate for the patient's educational and cultural background; consider metaphors within a narrative approach • Critically reflect on your own concepts of health and diabetes care and potential assumptions of Indigenous perspectives

priorities. These are embedded within a set of principles that recognize colonization as the predominant cause of health inequities for Indigenous peoples, health care equity as about providing appropriate resources according to need, and empowerment focused on building capacity with patients to address social drivers of disease. Within the framework, social factors (e.g. poverty, discrimination) are positioned as patient barriers to improved diabetes outcomes, while cultural factors facilitate improved clinical relationships and patient capacity. The framework, therefore, provides a lens to understand, identify and apply opportunities for augmenting patient capacity for change. As authors, we emphasize the relevance of this framework and, therefore, provide a synopsis and clinical vignette within this chapter in order to aid clinicians to explore its possibilities for clinical practice. Readers are invited to access E4E publications for more in-depth information around the evidence and consultation process supporting the framework (Table 1).

Improving diabetes outcomes for Indigenous peoples with diabetes includes the need for organizational enhancements and team-based approaches, but is limited by the reality of health-care human resources in many Indigenous communities. Health-care personnel gaps appear to be filled by expanding the roles of existing front-line staff. While prevention strategies must consider cultural elements and the influence of inequities on diabetes outcomes, so too must clinical service. The following section provides a description of an approach to care that integrates key aspects of the complex associations between cultural contexts and social inequities that frame diabetes within Indigenous populations.

Social Barriers to Desired Diabetes Outcomes

Understanding social factors that influence diabetes of Indigenous populations assists health-care providers in providing care that: 1) addresses barriers to desired diabetes outcomes; 2) better achieves management/therapeutic goals; and 3) fosters self-efficacy and health with patients.

Social and economic resource disparities

Material deprivation within the social environment directly impacts diabetes. Relationships between resource limitations, socioeconomic status, and the social environment directly impact diabetes through material deprivation. Indirectly, psychosocial pathways, such as stress, depression, anxiety and loss of control, further undermine health outcomes. This requires health-care providers to recognize socioeconomic disadvantage as a normalized state for many Indigenous peoples, limiting choices, increasing levels of stress, and diminishing capacity for self-care and lifestyle change. Attention for limited resources among families is key to recognizing the contexts in which self-care occurs. Limited budgets for food and financial sharing result in the diversion of resources, making family an important source of support as well as a key stressor.

Accumulation of adverse life experiences

Persistent and recurring experiences of adversity accumulate, influencing wellness and health. These diminish resilience and capacity to cope with disease. Health-care providers should keep in mind that adversity and support are complex and often ambiguous. The impact of residential schools not only persists among traumatized individuals, but the system continues to adversely influence health behaviours that impact others.

Colonization, inequity and health care

Given the context of historical relationships, social exclusion and trauma experienced by Indigenous persons, clinical approaches that establish physician authority, expertise, status and professional distance can negatively impact physician-patient relationships. Health-care providers should recognize unequal treatment as a reality in Canada's health system. This plays out for Indigenous peoples in heightened awareness and reaction when power and authority are expressed in the physician-patient relationship.

Facilitating Outcomes Using a Cultural Approach

Viewing culture as a protective mechanism involves moving beyond envisioning Indigenous peoples' experience of health and illness from the patient's cultural lens alone, in order to understand and support a patient's own preferences and connections to cultural resources.

Culture is therapeutic

As health is positively correlated with a sense of security in cultural identity, accessing cultural knowledge and traditions means that culture is protective for many Indigenous peoples. While Indigenous peoples vary in how they connect with traditional worldviews,

traditional medicine and ceremony are widely desired for accessing and re-connecting to culture in conjunction with Western medicine. Many Indigenous people do not talk about traditional medicines or practices with health-care providers, possibly due to incongruence between these knowledge systems, as well as persistent mistrust and fear of reprisal from health-care providers.

Culture informs relationships

Cultural perspectives inform how patients experience diabetes and engage with health care. Patient resistance may reflect the need for health-care providers to focus on relationship-building strategies. Patients and health-care providers have a mutual interest in getting to know one another better. Health-care providers who pay attention to issues of process and pace can help patients meet their desire to be treated with respect and without judgment; it can also allow health-care providers to move toward safer and more inviting environments that foster sharing. An Indigenous person's experiences of diabetes and its care are also embedded in connectedness to others, particularly family dynamics and community supports and structures, of which patient-provider relationships and interprofessional health-care teams are a part.

Culture frames knowledge

Through contextualization and exchange between health-care providers and patients, greater attention can be paid to reaching mutual understanding. Failing to elicit and address the patient's social and cultural contextual factors silences patient perspective and eliminates opportunity to ground clinical management approaches within a patient-centred approach, potentially exacerbating negative outcomes. Limitations of diabetes and general health literacy stemming from inadequate access to education may hinder the Indigenous person's abilities to engage with health and diabetes management recommendations. Conversely, placing diabetes care knowledge within the cultural, social and political landscape of Indigenous peoples can facilitate patient engagement with accessing diabetes knowledge. Effective communication for achieving knowledge exchange and patient education integrates intercultural communication strategies.

It is not acceptable to presume that Indigenous people are uninterested in the physiology of diabetes when, in reality, they report wanting to understand what causes diabetes and how to manage the illness. Health-care providers need to recognize stressors that adversely impact learning, draw on sources of health information actually available to patients (in professional, popular and folk realms) (122), mitigate resistance to health information due to health-care provider–patient relationship discord, and foster modes of knowledge transmission appropriate for the social and cultural context.

Key Concepts for Application of the E4E Care Framework

Patient-centred care (125), cultural competency and cultural safety (126) appear to be critical for quality care with Indigenous peoples, but are also broad concepts that require interpretation. The E4E framework posits that improving health outcomes for Indigenous peoples involves addressing historical and contextual factors in which disease and illness occur, while healing distrust in the Canadian health-care system. This moves beyond merely defining cultural competency as a list of patient beliefs and behaviours for clinicians, toward structural competency (127) that requires critical consciousness of social factors driving disease and wellness. It also highlights the fundamental role of anti-racism in the equitable delivery of health care (128,129). On top of these are layered notions of authentic inclusion grounded in Indigenous cultural approaches, moving providers toward vital relational and culturally-informed aspects of care that enable the facilitation of improved diabetes outcomes.

The E4E framework provides knowledge and recommendations for use as a motivational interviewing (130) approach within the clinical interaction that unpacks the described complex concepts. This approach aims to leverage patient motivation for health promoting behaviour change, among other things by engaging "open-ended questions, reflective listening, and support for patient autonomy and self-efficacy" (130) to overcome ambivalence, resistance and avoidance around disease management. As described in the E4E vignette, patient engagement is facilitated by screening for resource limitations influencing diabetes onset, as well as exploring with patients their perspectives on adversities that undermine one's capacity to manage diabetes. Notably, trauma informed relational work (131) that seeks to address power imbalance, authoritarian approaches and a history of mistrust is the critical first step that enables patient engagement.

RECOMMENDATIONS

1. Management of prediabetes and diabetes in Indigenous populations should follow the same clinical practice guidelines as those for the general population with respect for, and sensitivity to, particular social, historical, economic, cultural and geographic issues as they relate to diabetes care and education [Grade D, Consensus].

2. Starting in early childhood, Indigenous individuals should be evaluated for modifiable risk factors of diabetes (e.g. obesity, inactivity, unhealthy diet), prediabetes or metabolic syndrome [Grade D, Consensus] (see Type 2 Diabetes in Children and Adolescents chapter, p. S247).

3. Screening for diabetes in Indigenous populations should follow guidelines for high-risk populations (i.e. younger, including children, and at more frequent intervals depending on presence of additional risk factors) [Grade D, Consensus] (see Screening for Diabetes in Adults chapter, p. S16; Type 2 Diabetes in Children and Adolescents chapter, p. S247.

4. To promote access to screening for remote Indigenous populations, access to standard laboratory testing is recommended; in its absence, point of care testing for A1C may be considered where testing is associated with a quality control program; and interpretation and follow-up expertise is available [Grade D, Consensus].

5. Retinal photography screening programs may be used in Indigenous communities living in remote areas to promote access to screening [Grade B, Level 2 (76)] (see Retinopathy chapter, p. S210).

6. Attainment of a healthy body weight prior to conception should be promoted among Indigenous women to reduce their risk for GDM [Grade D, Consensus]. Nutrition counseling should be provided on healthy eating and prevention of excessive weight gain in early pregnancy, ideally before 15 weeks of gestation, to reduce the risk of GDM [Grade D, Consensus] (see Diabetes and Pregnancy chapter, p. S255).

7. Indigenous women identified as being at risk for type 2 diabetes who are planning a pregnancy should:
   a. Be screened for diabetes using FPG and/or A1C [Grade D, Consensus] (see Screening for Diabetes in Adults chapter, p. S16).
   b. If identified as having diabetes, receive preconception counseling that includes optimal diabetes management, including nutrition and physical activity advice, preferably in consultation with an interprofessional pregnancy team to optimize maternal and neonatal outcomes [Grade D, Consensus] (see Diabetes and Pregnancy chapter, p. S255).

8. Pregnant Indigenous women identified as being at risk for type 2 diabetes should:
   a. Be offered screening with an A1C test at the first antenatal visit, if not screened preconception [Grade D, Consensus] (see Diabetes and Pregnancy chapter, p. S255].

9. Pregnant Indigenous women with diabetes should:
   a. Receive management following the same clinical practice guidelines as those for the general population to improve pregnancy outcomes [Grade D, Consensus].

10. Postpartum:
   a. Indigenous women with pre-existing diabetes or GDM should be encouraged to breastfeed immediately to reduce the risk of neonatal hypoglycemia [Grade D, Consensus] (see Diabetes and Pregnancy chapter, p. S255).
   b. The infant of a pregnant Indigenous woman with diabetes should receive close monitoring for neonatal hypoglycemia with capillary blood glucose monitoring for up to 36 hours [Grade D, Consensus].
   c. Indigenous women with GDM should be screened with a 75 g OGTT between 6 weeks and 6 months postpartum to detect prediabetes and diabetes [Grade D, Consensus] (see Diabetes and Pregnancy chapter, p. S255)] and regularly thereafter according to recommendations in Screening for Diabetes in Adults chapter, p. S16].

11. Indigenous communities should be supported in initiating and maintaining culturally appropriate primary prevention programs for children and adults to assess and mitigate risk factors such as:
   a. Geographic and cultural barriers [Grade D, Consensus]
   b. Food insecurity [Grade D, Consensus]
   c. Psychological stress [Grade D, Consensus]
   d. Insufficient infrastructure [Grade D, Consensus]
   e. Settings that are not conducive to physical activity [Grade D, Consensus]

Abbreviations:
A1C, glycated hemoglobin; *ADI*, Aboriginal Diabetes Initiative; *BG*, blood glucose; *BP*, blood pressure; *CV*, cardiovascular; *CKD*, chronic kidney disease; *ESRD*, end stage renal disease; *GDM*, gestational diabetes; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *PCOS*, polycystic ovary syndrome; *POC*, point of care.

Other Relevant Guidelines

Screening for Diabetes in Adults, p. S16
Reducing the Risk of Developing Diabetes, p. S20
Organization of Diabetes Care, p. S27
Monitoring Glycemic Control, p. S47
Weight Management in Diabetes, p. S124
Cardiovascular Protection in People with Diabetes, p. S162
Treatment of Hypertension, p. S186
Chronic Kidney Disease in Diabetes, p. S201
Retinopathy, p. S210
Foot Care, p. S222
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255

Related Websites

First Nation, Inuit and Aboriginal Health. http://www.hc-sc.gc.ca/fniah-spnia/diseases-maladies/diabete/index-eng.php. Accessed March 21, 2017.

National Aboriginal Diabetes Association. http://www.nada.ca. Accessed March 21, 2017.

Author Disclosures

No authors have anything to disclose.

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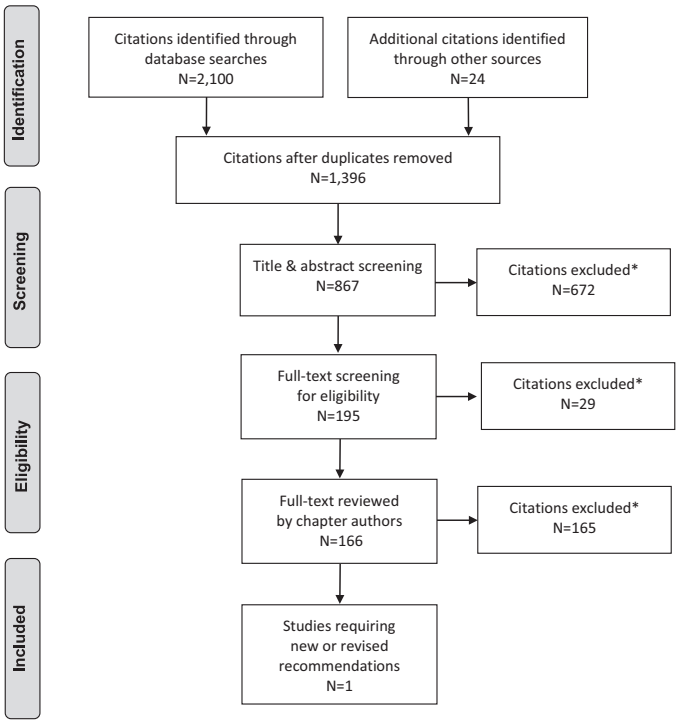
Literature Review Flow Diagram for Chapter 38: Type 2 Diabetes and Indigenous Peoples



*Excluded based on: population, intervention/exposure, comparator/control or study design.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 (132).

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Appendix 1

Diabetes Canada Diabetes Charter

DIABETES CHARTER FOR CANADA

The vision of Diabetes Canada for the Diabetes Charter for Canada is a country where people with diabetes live to their full potential.

The guiding principles of Diabetes Canada in developing this Charter are to:
- Ensure that people who live with diabetes are treated with dignity and respect.
- Advocate for equitable access to high quality diabetes care and supports.
- Enhance the health and quality of life for people who live with diabetes and their caregivers.

Canadians Living with Diabetes* Have the Right to:
- Be treated with respect, dignity, and be free from stigma and discrimination.
- Affordable and timely access to prescribed medications, devices, supplies and high quality care, as well as affordable and adequate access to healthy foods and recreation, regardless of their income or where they live.
- Timely diagnosis followed by education and advice from an interprofessional team which could include the primary care provider, diabetes educator, nurse, pharmacist, dietitian and other specialists.
- Emotional and mental health support, as well as support for their caregivers, if needed.
- Be an active partner in decision making with their health-care providers.
- Have access to their medical records and other health information when requested, and have it easily understood.
- Diabetes information, education and care that take into account a person's age, culture, religion, personal wishes, language and schooling.
- Have their eyes, feet, kidneys, blood glucose control, cardiovascular risk factors and mental health checked as often as recommended by current clinical practice guidelines.
- Affordable access to insurance coverage.
- Fully participate in daycare, pre-school, school and extracurricular activities, receiving reasonable accommodation and assistance, if needed.
- Supportive workplaces that do not discriminate and make reasonable accommodation, as needed.
- Appropriate and seamless transitional care that recognizes the progression of the disease.

Canadians Living with Diabetes Have the Responsibility to:
- Self-manage to the best of their ability and personal circumstances, including a healthy diet, exercise, following care plans and attending appointments.
- Be honest and open with health providers about their current state of health so that the most suitable care plans can be created.
- Actively seek out education, information and support to live well with diabetes.
- Respect the rights of other people with diabetes and health-care providers.

Governments Have the Responsibility to:
- Form comprehensive policies and plans for the prevention, diagnosis and treatment of diabetes and its complications.
- Collect data on diabetes burden, such as costs and complications, and to regularly evaluate whether progress is being made.
- Guarantee fair access to diabetes care, education, prescribed medications, devices, and supplies to all Canadians, no matter what their income or where they live.
- Address the unique needs and disparities in care and outcomes of vulnerable populations who experience higher rates of diabetes and complications and significant barriers to diabetes care and support.
- Implement policies and regulations to support schools and workplaces in providing reasonable accommodation to people with diabetes in their self-management.

Health-Care Providers Have the Right to:
- Ongoing training, funding and tools needed to provide high quality diabetes care.
- Work in well-coordinated teams, either at the same location or virtually where support from specialists who provide diabetes care can be obtained within a reasonable time.

Health-Care Providers Have the Responsibility to:
- Treat people with diabetes as full partners in their own care.
- Learn and apply up-to-date evidenced-based clinical practice guidelines when caring for people with diabetes.
- Diagnose people living with diabetes as early as possible.
- Help people with diabetes and their caregivers navigate the health-care system.

Schools, Pre-schools, and Daycares Have the Responsibility to:
- Ensure staff and the child's peers have accurate information about diabetes, provide a safe environment for diabetes self-management and protect children with diabetes from discrimination.

Workplaces Have the Responsibility to:
- Create an environment where people can reach their full potential by providing accommodation and eliminating discrimination against people with diabetes.

Diabetes Canada Has the Responsibility to:
- Strongly advocate for the rights of people living with diabetes on behalf of Canada's diabetes community.
- Raise public awareness about diabetes.
- Work to ensure the accuracy of information about diabetes in the public domain.
- Partner with researchers to improve the planning, provision and quality of diabetes care by promoting and applying research.
- Advocate for equitable access to diabetes care, education, medications, devices and supplies.

*And their informal caregivers where relevant

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Appendix 2

Etiologic Classification of Diabetes Mellitus

Type 1 diabetes (including LADA form)

(Beta-cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated B. Idiopathic

Type 2 diabetes

(May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

Gestational diabetes mellitus

Other specific types

Genetic defects of beta-cell function
- Chromosome 20, HNF-4alpha (MODY1)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 12, HNF-1alpha (MODY3)
- Chromosome 13, IPF-1 (MODY4)
- Chromosome 17, HNF-1beta (MODY5)
- Chromosome 2, NeuroD1 (MODY6)
- Chromosome 2, KLF11 (MODY7)
- Chromosome 9, CEL (MODY8)
- Chromosome 7, PAX4 (MODY9)
- Chromosome 11, INS (MODY10)
- Chromosome 8, BLK (MODY11)
- Chromosome 11, ABCC8
- Chromosome 11, KCNJ11
- Mitochondrial DNA
- Permanent neonatal diabetes
- Transient neonatal diabetes
- Others

Genetic defects in insulin action
- Leprechaunism
- Lipoatrophic diabetes
- Rabson-Mendenhall syndrome
- Type A insulin resistance
- Others

Diseases of the exocrine pancreas
- Cystic fibrosis
- Fibrocalculous pancreatopathy
- Hemochromatosis
- Neoplasia
- Pancreatitis
- Trauma/pancreatectomy
- Others

Endocrinopathies
- Acromegaly
- Aldosteronoma
- Cushing's syndrome
- Glucagonoma
- Hyperthyroidism
- Pheochromocytoma
- Somatostatinoma
- Others

Drug or chemical induced
- Alpha-interferon
- Atypical antipsychotics*
- Beta-adrenergic agonists
- Calcineurin inhibitors*
- Diazoxide
- Dilantin
- Fluoroquinolones
- Glucocorticoids*
- Highly active antiretroviral therapy (HAART)*
- HMG CoA reductase inhibitors (statins)
- Nicotinic acid
- Pentamidine
- Thiazides
- Thyroid hormone
- Vacor (rodenticide)
- Others

Infections
- Congenital rubella
- Cytomegalovirus
- Others

Uncommon forms of immune-mediated diabetes
- Anti-insulin receptor antibodies
- "Stiff-man" syndrome
- Others

Other genetic syndromes sometimes associated with diabetes
- Down syndrome
- Friedreich's ataxia
- Huntington chorea
- Klinefelter syndrome
- Laurence-Moon-Bardet-Biedl syndrome
- Myotonic dystrophy
- Porphyria
- Prader-Willi syndrome
- Turner syndrome
- Wolfram syndrome
- Others

Adapted and updated from: American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;35(suppl 1):S64-71.
LADA; latent autoimmune diabetes of adults
* Medications more commonly associated with hyperglycemia.

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Appendix 3

Sample Diabetes Patient Care Flow Sheet for Adults

Type of diabetes: ☐ Type 1 ☐ Type 2 ☐ Other **Date Diagnosed:**			**Patient Name:**	
Comorbidities: ☐ Hypertension ☐ Dyslipidemia ☐ CKD - stage _____ ☐ Coronary artery disease ☐ Peripheral arterial disease ☐ Stroke/TIA ☐ Depression/Anxiety ☐ Other(s):			**Date of Birth:**	
		Date:	**Date:**	**Date:**
Healthy behaviour interventions	**Weight** (kg) **Height** (cm) **BMI** **Waist circumference** (cm)	Wt _____ Ht _____ BMI _____ WC _____	Wt _____ Ht _____ BMI _____ WC _____	Wt _____ Ht _____ BMI _____ WC _____
	Nutrition			
	Physical Activity (Aerobic 150 mins/week, Resistance 2-3x/week)			
	Smoking Status	☐ Non-smoker ☐ Ex-smoker ☐ Smoker	☐ Non-smoker ☐ Ex-smoker ☐ Smoker	☐ Non-smoker ☐ Ex-smoker ☐ Smoker
Glycemic control	**A1C** (target: ≤7% or _____ %) (Individualize based on patient characteristics and antihyperglycemic medication(s) – see CPG) (q3 months. If at target and stable - q6 months)	Test Date: Result:	Test Date: Result:	Test Date: Result:
	Antihyperglycemic Medication(s) **Drug Name(s)/Dose(s):**			
	Therapy Adherence/Concerns			
	BG Record (targets: premeal: 4-7 mmol/L or _____ mmol/L; 2hr postmeal: 5-10 mmol/L or _____ mmol/L) (Individualize based on ability to achieve A1C target + risk of hypoglycemia) (Annual fasting glucose meter/lab comparison)	 Meter/Lab	 Meter/Lab	 Meter/Lab
	Hypoglycemic Episodes (frequency/pattern/driving risk)			
CV Risk Assessment and Management	**BP** (target <130/80 mmHg, 3 readings recommended) **Pulse**			
	Antihypertensive(s) **Drug Name(s)/Dose(s):**			
	CVD Symptoms (angina, decreased exercise tolerance, SOB, HF symptoms, claudication)	☐ None ☐ Yes	☐ None ☐ Yes	☐ None ☐ Yes
	Resting ECG, every 3-5 yrs If any: age >40 yrs; duration of diabetes >15 yrs + age >30 years; end organ damage (microvascular, CV); >1 CV risk factor(s)	Date: Report:	Date: Report:	Date: Report:
	Lipids (primary target: LDL <2.0 mmol/L or >50% reduction in LDL, or non-HDL <2.6 mmol/L or apo B <0.8 g/L)	LDL-C non-HDL-C test date:	LDL-C non-HDL-C test date:	LDL-C non-HDL-C test date:
	Lipid-lowering Therapy **Statin +/- 2nd line agent(s)** **Drug Name(s)/Dose(s):** (If any: clinical CVD; age ≥40 yrs; age <40 yrs + 1 of the following: diabetes duration >15 yrs and age >30 yrs; microvascular complications; warrants therapy based on presence of other risk factors according to 2016 CCS Lipid Guidelines)	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:
	ACE inhibitor/ ARB **Drug Name(s)/Dose(s):** If any: clinical CVD; age >55 yrs with an additional CV risk factor or end organ damage (albuminuria, retinopathy, LVH); microvascular complications	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:

https://doi.org/10.1016/j.jcjd.2017.10.042

		Date:	Date:	Date:
	Antihyperglycemic Agent with Demonstrated CV Outcome Benefit **Drug Name(s)/Dose(s):** (If type 2 DM with clinical CVD not at glycemic target - empagliflozin, liraglutide, canagliflozin)	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:	☐ Continue ☐ Start ☐ No – reason:
	Antiplatelet Agent(s) **Drug Name(s)/Dose(s):** (If established CVD; consider if additional CV risk factors)	☐ Not indicated ☐ Yes	☐ Not indicated ☐ Yes	☐ Not indicated ☐ Yes
CKD	**Urine ACR** (normal <2 mg/mmol)	Test Date: Result:	Test Date: Result:	Test Date: Result:
CKD	**Serum Creatinine/eGFR**	Test Date: Result:	Test Date: Result:	Test Date: Result:
CKD	**CKD**	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Retinopathy	**Dilated Eye Exam** (type 1 – annually; type 2 – q1-2 years or as recommended by vision care professional)	☐ Date of last visit: ☐ Reminded	☐ Date of last visit: ☐ Reminded	☐ Date of last visit: ☐ Reminded
Retinopathy	**Retinopathy**	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Retinopathy	**Severity/Therapies**			
Neuropathy	**Neuropathy Symptoms** (e.g. pain, paresthesia, GI symptoms, sexual dysfunction)	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Neuropathy	**Diabetic Foot Exam** (includes 10 g monofilament or 128 Hz tuning fork, structural abnormalities, skin changes, pulses) (annually for screening; every visit if diabetic foot complications) See Appendices 11A, 11B and 12	Sensation _____ Pulses _____ Skin _____ Other _____	Sensation _____ Pulses _____ Skin _____ Other _____	Sensation _____ Pulses _____ Skin _____ Other _____
Neuropathy	**Neuropathy**	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Mental Health	**Screen for Depression, Anxiety, Other Stressors** (consider use of PHQ-9, GAD-7)	Concerns:	Concerns:	Concerns:
Vaccination	**Influenza** (annual)	☐ No ☐ Yes Reason: Date:	☐ No ☐ Yes Reason: Date:	☐ No ☐ Yes Reason: Date:
Vaccination	**Pneumococcal** (once; repeat if >65 yrs)	☐ Yes Date:	☐ No Reason:	
Management Plans	**Patient Goals** **Barriers to Self-management** (e.g. coverage, accessibility, competing demands)			
Management Plans	**Women** Contraception/preconception planning			
Management Plans	**Driving Guidelines Reviewed**			
Management Plans	**Sick-Day Management** (advise holding metformin, SGLT2i, SU, ACEi/ARB, diuretic, NSAIDs if inadequate fluid intake and ill			
Management Plans	**Referrals Made**			
Management Plans	**Changes to Medications or Other Management**			
Management Plans	**Resources Provided**			
	RECALL (usually q3-4 months)	☐ Appointment given ☐ Noted in recall system	☐ Appointment given ☐ Noted in recall system	☐ Appointment given ☐ Noted in recall system

For additional diabetes management resources, visit **www.guidelines.diabetes.ca.**

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Appendix 4

Smarter Step Count Prescription

Health-Care Provider Guidelines

Suggest step count increments at each clinic visit to reach goal (an increase of 3,000 steps per day above the baseline step count within 1 year).

Steps per day at baseline	Clinic Visit 1 (0 months)	Clinic Visit 2 (3 months)	Clinic Visit 3 (6 months)	Clinic Visit 4 (9 months)
<5,000	+500	+750	+750	+1,000
5,000–7,499	+750	+1,000	+1,250	
≥7,500	+1,000/+2,000	+1,000		

Start Date:

Patient's Name:

Baseline Step Count: _____ Recommended Step Count: _____

Clinic Visit Number: _____ Start Date for Step Increase: _____

Patient Step Count Prescription

Today's Date:

Patient's Name:

- Please try to complete at least _____ steps per day until your next clinic visit.
- Please record your step counts in your log sheets at the end of each day.
- Please bring your log sheets to the next clinic visit which will be in about three months.

Physician's Name:

Physician's Signature:

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Appendix 5

Self-Monitoring of Blood Glucose (SMBG) Recommendation Tool for Health-Care Providers

Basic SMBG requirements (must be met)

The person with diabetes (or a family member/caregiver) must have the knowledge and skills to use a home blood glucose monitor and to record the results in an organized fashion.

The person with diabetes and/or members of the health-care team must be willing to review and act upon the SMBG results in addition to the glycated hemoglobin (A1C) results.

A. REGULAR SMBG is required if the person with diabetes is:

SITUATION	SMBG RECOMMENDATION
Using basal-bolus insulin injection therapy of insulin (≥4 times per day)	SMBG ≥4 times per day (see page 2 – 4 times per day – [basal-bolus])
Using CSII (insulin pump)	
Using insulin <4 times per day	SMBG at least as often as insulin is being given (see page 2 – premixed or basal insulin only)
Pregnant (or planning a pregnancy), whether using insulin or not	SMBG individualized and may involve SMBG ≥4 times per day
Hospitalized or acutely ill	
Starting a new medication known to cause hyperglycemia (e.g. steroids)	SMBG individualized and may involve SMBG ≥2 times per day
Experiencing an illness known to cause hyperglycemia (e.g. infection)	

B. INCREASED FREQUENCY OF SMBG may be required if the person with diabetes is:

SITUATION	SMBG RECOMMENDATION
Using drugs known to cause hypoglycemia (e.g. sulfonylureas, meglitinides)	SMBG at times when symptoms of hypoglycemia occur or at times when hypoglycemia has previously occurred
Has an occupation that requires strict avoidance of hypoglycemia	SMBG as often as is required by employer
Not meeting glycemic targets	SMBG ≥2 times per day, to assist in healthy behaviour interventions and/or medication changes until such time as glycemic targets are met
Newly diagnosed with diabetes (<6 months)	SMBG ≥1 time per day (at different times of day) to learn the effects of various meals, exercise and/or medications on blood glucose
Treated with healthy behaviour interventions and noninsulin antihyperglycemic agents and is meeting glycemic targets	Some people with diabetes might benefit from very infrequent checking (SMBG once or twice per week) to ensure that glycemic targets are being met between A1C tests

C. DAILY SMBG is NOT usually required if the person with diabetes:

Is treated only with healthy behaviour interventions and is meeting glycemic targets

Has prediabetes

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Suggested SMBG Patterns for People Using Insulin

Basal Insulin Only – NPH or long-acting insulin analog, typically given at bedtime. *SMBG at least as often as insulin is being given.* Optional, less frequent SMBG can be done at other times of day to ensure glycemic stability throughout the day.

	BREAKFAST		LUNCH		SUPPER		BEDTIME	NIGHT
	before	after	before	after	before	after		
Insulin							NPH/long-acting	
SMBG pattern	**SMBG test**							
Adjustment	Basal insulin ↑ if BG high ↓ if BG low							

Premixed – typically given pre-breakfast and pre-supper. *SMBG at least as often as insulin is being given.* SMBG QID until glycemic targets are met; SMBG BID (alternating times) is usually sufficient once glycemic targets are met.

	BREAKFAST		LUNCH		SUPPER		BEDTIME	NIGHT
	before	after	before	after	before	after		
Insulin	pre-mixed				pre-mixed			
SMBG pattern 1: Starting	**SMBG test**		**SMBG test**		**SMBG test**		**SMBG test**	
SMBG pattern 2: Stable Alternating daily	**SMBG test**				**SMBG test**			
			SMBG test				**SMBG test**	
Adjustment	Pre-supper insulin ↑ if BG high ↓ if BG low		Pre-breakfast insulin ↑ if BG high ↓ if BG low		Pre-breakfast insulin ↑ if BG high ↓ if BG low		Pre-supper insulin ↑ if BG high ↓ if BG low	

Basal-bolus injection therapy or CSII – typically given as rapid-acting insulin (bolus) before each meal and NPH or long-acting analogue (basal) typically given at bedtime or as rapid-acting insulin with insulin pump. SMBG should be QID, pre-meal and bedtime, in order to assess previous dose and to adjust next dose. Some people with diabetes find that post-prandial checking can also be helpful.

	BREAKFAST		LUNCH		SUPPER		BEDTIME	NIGHT
	before	after	before	after	before	after		
Insulin	rapid/ (bolus)		rapid/ (bolus)		rapid/ (bolus)		NPH/long-acting	
SMBG pattern 1: Starting or stable	**SMBG test**		**SMBG test**		**SMBG test**		**SMBG test**	
SMBG pattern 2: Stable, focus on postmeal BG	**SMBG test**	**SMBG test**		**SMBG test**		**SMBG test**		
SMBG pattern 3: Intensive management	**SMBG test**	**SMBG test**	**SMBG test**	**SMBG test**	**SMBG test**	**SMBG test**	**SMBG test**	**SMBG test**
Adjustment	Basal insulin ↑ if BG high ↓ if BG low	Pre-breakfast insulin ↑ if BG high ↓ if BG low		Pre-lunch insulin ↑ if BG high ↓ if BG low		Pre-supper insulin ↑ if BG high ↓ if BG low		Basal insulin ↓ if BG low

BG, blood glucose; *CSII,* continuous subcutaneous insulin infusion; *SMBG,* self-monitoring of blood glucose

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Appendix 6

Types of Insulin

Types of insulin			
Insulin type (trade name)	**Onset**	**Peak**	**Duration**
Bolus (preprandial or mealtime) insulins			
Rapid-acting insulin analogues (clear) • Insulin aspart (NovoRapid®) • Insulin glulisine (Apidra®) • Insulin lispro (Humalog®) U-100 U-200 • Faster-acting insulin aspart (Fiasp®)	 9–20min 10–15min 10–15min 4min	 1–1.5h 1–1.5h 1–2h 0.5-1.5h	 3–5h 3.5–5h 3–4.75h 3-5h
Short-acting insulins (clear) • Insulin regular [Humulin®-R, Novolin® ge Toronto] • Insulin regular [Entuzity® (U-500)]	 30min 15min	 2–3h 4-8h	 6.5h 17-24h
Basal insulins			
Intermediate-acting (cloudy) • Insulin neutral protamine Hagedorn (Humulin® -N, Novolin® ge NPH)	1–3h	5–8h	Up to 18h
Long-acting insulin (clear) • Insulin detemir (Levemir®) • Insulin glargine U-100 (Lantus®) • Insulin glargine U-300 (Toujeo®) • Insulin glargine biosimilar (Basaglar®) • Degludec U-100, U-200 (Tresiba®)	90min	Not applicable	U-100 glargine 24h, detemir 16–24h U-300 glargine >30h degludec 42h
Premixed insulins			
Premixed regular insulin –NPH (cloudy) • Humulin® 30/70 • Novolin® ge 30/70, 40/60, 50/50	A single vial or cartridge contains a fixed ratio of insulin		
Premixed insulin analogues (cloudy) • Biphasic insulin aspart (NovoMix® 30) • Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)	(% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Data represents estimations derived from pooled data analysis using various experimental conditions. There is significant inter- and intra-individual variation in pharmacokinetics and pharmacodynamics depending on a variety of clinical factors, including dose. Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association; Ottawa, Ontario, Canada) and product monographs for detailed information.			

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Appendix 7

Therapeutic Considerations for Renal Impairment

Medication	CKD 3A (eGFR 45-59mL/min)	CKD 3B (eGFR 30-44 mL/min)	CKD 4 (eGFR 15-29 mL/min)	CKD 5 (eGFR <15 mL/min or dialysis)
Metformin‡	Dose adjustment not required	Reduce dose (500-1,000 mg/day) Do not initiate, can maintain	Use alternative agent due to risk of accumulation	
GLP-1 receptor agonists				
Dulaglutide	Dose adjustment not required			Caution as safety not established
Exenatide/ Exenatide ER	Dose adjustment not required (>50 mL/min)	Caution (30-50 mL/min)	Use alternative agent due to risk of accumulation	
Lixisenatide	Dose adjustment not required		Use alternative agent as safety not established	
Liraglutide	Dose adjustment not required			Use alternative agent as safety not established
SGLT2 inhibitors				
Canagliflozin‡	Can maintain at 100 mg daily, do not initiate for glycemic control. May be initiated when indicated for CV and renal protection*	Use alternative agent because of limited glycemic efficacy. May be considered when indicated for CV and renal protection*	Use alternative agent due to lack of glycemic efficacy	
Dapagliflozin‡	Use alternative agent due to lack of glycemic efficacy			
Empagliflozin‡	Can maintain, do not initiate for glycemic control. May be initiated when indicated for CV and renal protection*	Use alternative agent because of limited glycemic efficacy. May be considered when indicated for CV and renal protection*	Use alternative agent due to lack of glycemic efficacy	
DPP-4 Inhibitors				
Alogliptin	Lower dose 12.5 mg daily		Lower dose 6.25 mg daily	
Linagliptin	Dose adjustment not required			Caution as safety not established
Saxagliptin	Dose adjustment not required (>50 mL/min)	Lower dose 2.5 mg daily (<50 mL/min)		Use alternative agent as unproven efficacy for patients requiring hemodialysis
Sitagliptin	Dose adjustment not required (≥50 mL/min)	Lower dose 50 mg daily (30-49 mL/min)	Lower dose 25 mg daily	
Alpha-glucosidase inhibitor				
Acarbose	Dose adjustment not required		Consider alternative agent as safety not established	
Meglitinides				
Repaglinide	Consider lower doses due to risk of hypoglycemia		Consider lower doses and beware of extended duration of action due to risk of hypoglycemia	
Sulfonylureas				
Gliclazide‡	Caution due to risk of hypoglycemia		Use alternative agent due to risk of accumulation and hypoglycemia	
Glimepiride‡	Caution due to risk of hypoglycemia		Use alternative agent due to risk of accumulation and hypoglycemia	
Glyburide‡	Use alternative agent due to risk of accumulation and hypoglycemia			
Thiazolidinediones				
Rosiglitazone / Pioglitazone	Dose adjustment not required but caution as may lead to fluid retention			
Insulins	Dose adjustment not required		Consider lower doses and beware of extended duration of action due to risk of hypoglycemia	

*Limited glycemic efficacy but may be considered to reduce progression of nephropathy or for CV protection where indicated for individuals with eGFR >30mL/min (see recommendations).
‡These medications should be held during intercurrent illness - see Appendix 8. Sick Day Medication List.
Dose adjustment is not recommended for the antihyperglycemic agents listed above in CKD stages 1 and 2.
For full details on monitoring, please see product mongraphs.

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Appendix 8

Sick-Day Medication List

Instructions for Health-Care Professionals:
If people with diabetes become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:
- Angiotensin-converting enzyme inhibitors
- Angiotensin receptor blockers
- Direct renin inhibitors
- Nonsteroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B) Have reduced clearance and increase risk for adverse effects:
- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas
A ACE inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N nonsteroidal anti-inflammatory
S SGLT2 inhibitors

Please complete the following card and give it to your patient.

People with diabetes should be instructed that increased frequency of self blood glucose monitoring will be required, and adjustments to their doses of insulin or noninsulin antihyperglycemic agents may be necessary.

Instructions for People with Diabetes
When you are ill, particularly if you become dehydrated (e.g. vomiting or diarrhea), some medicines could cause your kidney function to worsen or result in side effects.

If you become sick and are unable to drink enough fluid to keep hydrated, you should **STOP** the following medications:

- Blood pressure pills
- Water pills
- Metformin
- Diabetes pills
- Pain medications
- Nonsteroidal anti-inflammatory drugs (see below)

_____

_____

_____

_____

_____

Please be careful not to take nonsteroidal anti-inflammatory drugs (which are commonly found in pain medications [e.g. Advil] and cold remedies).

Please check with your pharmacist before using over-the-counter medications and discuss all changes in medication with your health-care professional.

Please increase the number of times you check your blood glucose levels. If they run too high or too low, contact your health-care professional.

If you have any problems, you can call:

_____

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Appendix 9

Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

All people starting insulin should be counseled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

Example A: Basal insulin (degludec U-100 or U-200, detemir, glargine U-100 or U-300, NPH) added to non-insulin antihyperglycemic agents

- Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L or individualized targets (e.g. 4.0 to 5.5 mmol/L if A1C target ≤7.0% not achieved; higher fasting BG targets may be considered in some people with diabetes where the goal of avoiding hypoglycemia is important, see Targets for Glycemic Control, p. S42).
- Individuals can be taught self-titration, or titration may be done in conjunction with a health-care provider.
- Suggested starting dose is 10 units once daily at bedtime.
- Suggested titration is 1 unit per day until target is reached. (Degludec should be titrated by 2 units every 3 to 4 days or 4 units once a week).
- A lower starting dose, slower titration and higher targets may be considered for elderly or normal-weight subjects.
- In order to safely titrate insulin, people with diabetes must perform self-monitoring of blood glucose at least once a day fasting.
- Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Noninsulin antihyperglycemic agents (especially insulin secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example B: Basal Plus Strategy - Adding bolus (prandial or mealtime) insulin (aspart, faster-acting insulin aspart, glulisine, lispro) once daily to optimized basal insulin therapy

- When intensification of insulin therapy is necessary, start one injection of mealtime insulin to either main meal or breakfast.
- Starting dose is 2 to 4 units and the person with diabetes can be taught self titration or dose increase can be done by health-care provider.
- To safely increase dose, blood glucose levels should be measured at least prior to insulin dose then titrated by 1 unit daily to either of the following targets.
  - 2-hour post-meal glucose of ≤8.0 mmol/L
  - pre-meal glucose of the next meal of 4.0 to 7.0 mmol/L.
- Important to keep carbohydrate intake constant and may consider reduction or discontinuation of insulin secretagogues

Example C: Basal-Bolus Insulin - Multiple Daily Injections Therapy

- Calculate total daily dose of 0.3 to 0.5 units/kg then distribute as follows:
  a. 40% of total insulin dose as basal insulin (degludec U-100 or U-200, detemir, glargine U-100 or U-300, NPH)
  b. 20% of total insulin as bolus (prandial) insulin 3 times per day using rapid-acting insulin analogue (aspart, faster-acting insulin aspart, glulisine, lispro).

Example D: Premixed Insulin (Humulin 30/70, Novolin 30/70, Humalog Mix 25, Humalog Mix 50, NovoMix 30, added to noninsulin antihyperglycemic agents

- Suggested starting dose is 5 to 10 units once or twice daily (prebreakfast and/or presupper).
- Suggested titration is 1 to 2 units added to prebreakfast dose and/or presupper dose daily until target BG values are reached based on prebreakfast and presupper BG readings.
- Prebreakfast premixed insulin achieves presupper target BG value (4.0 to 7.0 mmol/L).
- Presupper premixed insulin achieves target fasting BG value (4.0 to 7.0 mmol/L).
- 30/70 premixed insulin should be given 30 to 45 minutes before meals.
- Humalog Mix 25 or NovoMix 30 premixed insulin should be given immediately before eating.
- Stop increasing insulin doses when both target BG levels are reached.
- If both BG targets are not reached, continue to increase the relevant dose until both targets achieved.
- The individual needs to self-monitor BG at least twice daily to safely titrate insulin.
- Insulin dose should not be increased if the individual experiences 2 or more episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Noninsulin antihyperglycemic agents (especially insulin secretagogues) may need to be reduced or stopped at the start of this regimen or when daytime hypoglycemia occurs

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Sample Instructions for Patients With Type 2 Diabetes Who Are Starting and Adjusting Insulin

You will be taking insulin _____ at _____ .

It is important that you continue to take your other diabetes medications as prescribed unless you have been told to change the dose or stop them.

How to adjust your insulin dose

- Your target fasting blood glucose level is _____ mmol/L.
- You will inject _____ units of _____ at _____ .
- You will continue to increase your insulin dose by _____ unit(s) every _____ day(s) until your fasting blood glucose level is _____ mmol/L.
- Do not increase your insulin when your fasting blood glucose is _____ mmol/L.
- You should call for further instructions when your blood glucose reaches _____ mmol/L for 3 or more days: phone number _____ .
- A side effect of insulin is low blood glucose (hypoglycemia); low blood glucose can occur with too much insulin, increased activity or not enough food.

Monitoring your blood glucose

- It is important to test your blood glucose while your insulin treatment is being modified.
- You should test your blood glucose and record the value every day before breakfast and _____ .
- Test before each meal, unless you are instructed differently.
- It is important to record your blood glucose values and any changes in activity or food in your diary and bring this to your next appointment; this information helps your diabetes health-care team understand your diabetes control.
- Unless otherwise instructed, you are trying to reach a target blood glucose of 4.0 to 7.0 mmol/L before meals, and 5.0 to 8.0 mmol/L after meals.
- If you think your blood glucose is low, check it and record that information in your diary.

Instructions for taking your other glucose-lowering diabetes medications:

Current medications	Dose	Time of day	Special instructions

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Appendix 10

Sample Diabetes and Driving Assessment Form

Sample Diabetes and Driving Assessment Form

Type of diabetes:

☐ type 1 ☐ type 2 ☐ other

Date Diagnosed:

_____

Diabetes treatment

☐ nutritional therapy/healthy behaviour interventions alone
☐ insulin
☐ sulfonylurea/meglinitide
☐ other noninsulin antihyperglycemic agent (metformin, alpha-glucosidase inhibitor, glitazone [TZD], GLP-1 receptor agonist, DPP-4 inhibitor or SGLT2 inhibitor)

Most recent A1C (within last 6 months)

☐ ≤7.0%
☐ 7.1–8%
☐ 8.1–11.9%
☐ ≥12%

Blood glucose monitoring

Is the driver with diabetes maintaining a log of their self-monitored blood glucose measurements with either a memory-equipped blood glucose meter or electronic record?
☐ Yes ☐ No

Are A1C results consistent with blood glucose logs?
☐ Yes ☐ No

For drivers on insulin or insulin secretagogues, is there evidence of blood glucose monitoring at least every 4 hours while driving or wearing of a continuous blood glucose monitoring device?
☐ Yes ☐ No

Hypoglycemia

Does the driver with diabetes have awareness of early symptoms of hypoglycemia (e.g. palpitations, shakiness, anxiety, sweating, hunger, tingling)?
☐ Yes ☐ No
Does the driver with diabetes know how to treat hypoglycemia?
☐ Yes ☐ No
For drivers with diabetes treated with insulin or insulin secretagogues, is blood glucose monitoring equipment and supplies of rapidly absorbable carbohydrate within easy reach in the vehicle?
☐ Yes ☐ No

For private drivers with diabetes, in the past 6 months, have there been any episodes of severe hypoglycemia

☐ while awake?
Specify number and date (s) _____
☐ while driving?
Specify number and date (s) _____
☐ while asleep?
Specify number and date (s) _____
Has the driver had evidence of hypoglycemia unawareness in the past 6 months?
☐ Yes ☐ No
If yes, has there been recovery of hypoglycemia awareness?
☐ Yes ☐ No

For commercial drivers with diabetes, in the past 12 months, have there been any episodes of severe hypoglycemia

☐ while awake?
Specify number and date (s) _____
☐ while driving?
Specify number and date (s) _____
☐ while asleep?
Specify number and date (s) _____
Has the driver had evidence of hypoglycemia unawareness in the past 6 months?
☐ Yes ☐ No
If yes, has there been recovery of hypoglycemia awareness?
☐ Yes ☐ No

General Health

Does the patient have any of the following complications to an extent that could impair his/her ability to drive safely?

☐ Retinopathy ☐ Neuropathy
☐ Chronic Kidney Disease ☐ Amputation
☐ Cardiovascular Disease ☐ Other

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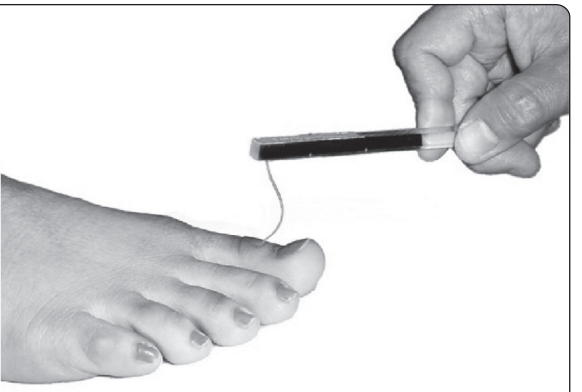
Appendix 11A

Rapid Screening for Diabetic Neuropathy Using the 10 g Semmes-Weinstein Monofilament

1. Show the 10 g Semmes-Weinstein monofilament to the patient.
2. Touch it first to the patient's forehead or sternum so that the sensation is understood.
3. Instruct the patient to say "yes" every time the monofilament stimulus is perceived.
4. With the patient's eyes closed, apply the monofilament to the dorsum of the great toe proximal to the nail bed as shown in the illustration. Use a smooth motion to touch the skin, bend the filament for a full second, then lift from the skin.



5. Perform this stimulus 4 times per foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
6. For each of the 8 stimuli, assign a score of 0 if it is not perceived, 0.5 if it is substantially less than that perceived on the forehead or sternum, and 1 if it is perceived normally. A score of 3 out of 8 correct responses means that the presence of neuropathy is likely. A score of 3.5 to 5 means that the risk of new-onset neuropathy in the next 4 years is high. A score of 5.5 or greater indicates that there is a low risk of neuropathy onset in the next 4 years.

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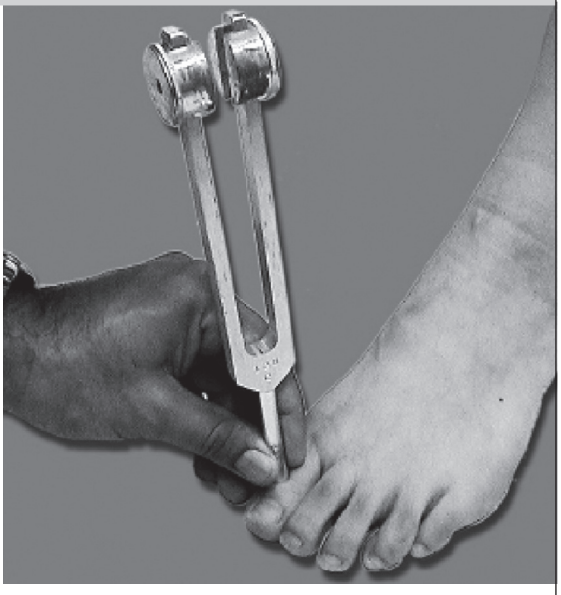
Appendix 11B

Rapid Screening for Diabetic Neuropathy Using the 128 Hz Vibration Tuning Fork (the "On-Off" Method)

Rapid Screening for Diabetic Neuropathy Using the 128 Hz Vibration Tuning Fork (The "On-Off" Method)

1. Strike the tuning fork against the palm of your hand hard enough that it will vibrate for approximately 40 seconds.
2. Apply the base of the tuning fork to the patient's forehead or sternum and ensure that the vibration sensation (not just the touch sensation) is understood.
3. With the patient's eyes closed, apply the tuning fork to the bony prominence situated at the dorsum of the first toe just proximal to the nail bed. Ask if the vibration sensation is perceived.
4. Ask the patient to tell you when the vibration stimulus has stopped, and then dampen the tuning fork with your other hand.
5. One point is assigned for each vibration sensation perceived (vibration "on"). Another point is assigned if the correct timing of dampening of the vibration is perceived (vibration "off ").
6. Repeat this procedure again on the same foot, then twice on the other foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.



7. Although this test can be used to rule out the presence of neuropathy, threshold scores do not exist to indicate the risk of future onset of neuropathy.

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Appendix 12

Monofilament Testing in the Diabetic Foot

Semmes-Weinstein Monofilament

Sensory examination should be carried out in a quiet and relaxed setting. First apply the monofilament on the patient's hands (or elbow or forehead) so that he or she knows what to expect.

The patient must not be able to see whether or where the examiner applies the filament. The three sites to be tested on both feet are indicated in Figure 1.

Apply the monofilament perpendicular to the skin surface (Figure 2a).

Apply sufficient force to cause the filament to bend or buckle (Figure 2b).

The total duration of the approach – skin contact and removal of the filament – should be approximately 2 seconds.

Apply the filament along the perimeter of, not on, an ulcer site, callus, scar or necrotic tissue.

Do not allow the filament to slide across the skin or make repetitive contact at the test site.

Press the filament to the skin and ask the patient whether they feel the pressure applied ('yes'/'no') and next where they feel the pressure ('left foot'/'right foot').

Repeat this application twice at the same site, but alternate this with at least one 'mock' application in which no filament is applied (total three questions per site).

Protective sensation is present at each site if the patient correctly answers two out of three applications. Protective sensation is absent with two out of three incorrect answers – the patient is then considered to be at risk of ulceration.

Encourage patients during testing by giving positive feedback.

The health-care provider should be aware of the possible loss of buckling force of the monofilament if used for too long a period of time.

Adapted from:
N. C. Schaper NC, Van Netten JJ, Apelqvist J, et al. Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev 2016; 32(Suppl. 1): 7–15.

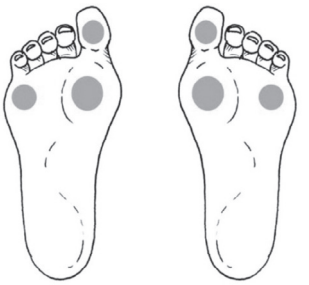
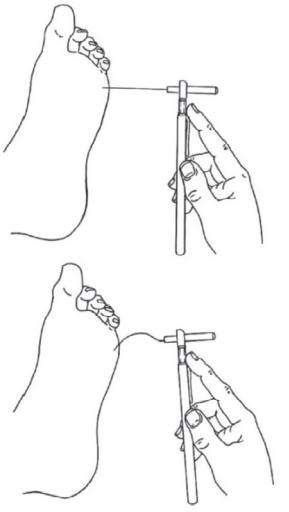


Figure 1. Sites to be tested with the monofilament



Figures 2a & 2b. Application of the monofilament

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Appendix 13

Diabetes and Foot Care: A Checklist

DO:

- check your feet every day for cuts, cracks, bruises, blisters, sores, infections or unusual markings.
- use a mirror to see the bottom of your feet if you can't lift them up.
- check the colour of your legs and feet. If there is swelling, warmth or redness or if you have pain, see your doctor or foot specialist right away.
- clean a cut or scratch with a mild soap and water and cover with a dry dressing for sensitive skin.
- trim your nails straight across.
- wash and dry your feet every day, especially between the toes.
- apply a good skin lotion every day on your heels and soles. Wipe off any excess lotion.
- change your socks every day.
- wear a good supportive shoe.
- wear professionally fitted shoes from a reputable store; professionally fitted orthotics may help.
- choose shoes with low heels (under 5 cm high).
- buy shoes in the late afternoon (since your feet swell slightly by then).
- avoid extreme cold and heat (including the sun).
- exercise regularly.
- see a foot care specialist if you need advice or treatment.

DO NOT:

- cut your own corns or calluses.
- treat your own in-grown toenails or slivers with a razor or scissors; see your physician/nurse practitioner or foot care specialist.
- use over-the-counter medications to treat corns and warts. They are dangerous for people with diabetes.
- apply heat to your feet with a hot water bottle or electric blanket; you could burn your feet without realizing it.
- soak your feet.
- take very hot baths.
- use lotion between your toes.
- walk barefoot inside or outside.
- wear tight socks, garters or elastics, or knee highs.
- wear over-the-counter insoles – they can cause blisters if they are not right for your feet.
- sit for long periods of time.
- smoke.

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Appendix 14

Diabetic Foot Ulcers—Essentials of Management

1. Assess underlying cause(s): neuropathy and/or ischemia.
2. Ulcers should be probed with a blunt-tipped instrument to detect sinus tracks or palpable bone suggestive of deep infections.
3. Plantar-surface ulcers require pressure relief. Individuals with plantar-surface foot ulcers should be nonweight-bearing as much as possible and utilize off-loading footwear or appliances (1).
4. Clinically noninfected ulcers do not routinely require cultures or antibiotics (2).
5. More serious infections in chronic foot ulcers tend to be polymicrobial and typically require empiric use of broad spectrum systemic antibiotics as soon as possible. Antibiotics can be subsequently tailored according to culture and sensitivity results. Cultures obtained by curettage or biopsy tend to be more reliable than surface swabs (3).
6. Wound bed preparation involves debridement of necrotic tissue (neuropathic wounds and noncritical ischemic wounds only) and maintenance of adequate moist wound environment with appropriate wound dressings. Hydrogels are used to increase wound bed moisture in dry or minimally draining neuropathic ulcers.
7. Comorbidities need to be managed (e.g. hyperglycemia).
8. Refer to a specialized wound clinic where available.

Modified from:

1. Lavery LA, Baranoski S, Ayello EA. Options for off-loading the diabetic foot. Adv Skin Wound Care 2004;17:181-6.
2. Lipsky BA, Berendt AR, Deery HG, et al; for the Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2004;39:885-910.
3. Frykberg RG, Zgonis T, Armstrong DG, et al; for the American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45(5 suppl):S1-66.

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Appendix 15

Glycated Hemoglobin Conversion Chart

National Glucose Standardization Program (NGSP) values (%) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) values (mmol/mol) based on the formula of IFCC = 10.93(NGSP)-23.50. Conversions are grouped according to each percentage point on the NGSP measurement scale. IFCC-standardised values are rounded to the nearest whole number.

5		6		7		8		9	
DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
5.0	31	6.0	42	7.0	53	8.0	64	9.0	75
5.1	32	6.1	43	7.1	54	8.1	65	9.1	76
5.2	33	6.2	44	7.2	55	8.2	66	9.2	77
5.3	34	6.3	45	7.3	56	8.3	67	9.3	78
5.4	36	6.4	46	7.4	57	8.4	68	9.4	79
5.5	37	6.5	48	7.5	58	8.5	69	9.5	80
5.6	38	6.6	49	7.6	60	8.6	70	9.6	81
5.7	39	6.7	50	7.7	61	8.7	72	9.7	83
5.8	40	6.8	51	7.8	62	8.8	73	9.8	84
5.9	41	6.9	52	7.9	63	8.9	74	9.9	85

10		11		12		13		14	
DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
10.0	86	11.0	97	12.0	108	13.0	119	14.0	130
10.1	87	11.1	98	12.1	109	13.1	120	14.1	131
10.2	88	11.2	99	12.2	110	13.2	121	14.2	132
10.3	89	11.3	100	12.3	111	13.3	122	14.3	133
10.4	90	11.4	101	12.4	112	13.4	123	14.4	134
10.5	91	11.5	102	12.5	113	13.5	124	14.5	135
10.6	92	11.6	103	12.6	114	13.6	125	14.6	136
10.7	93	11.7	104	12.7	115	13.7	126	14.7	137
10.8	95	11.8	105	12.8	116	13.8	127	14.8	138
10.9	96	11.9	107	12.9	117	13.9	128	14.9	139

https://doi.org/10.1016/j.jcjd.2017.10.051