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Roche

Frontiers in DIABETES

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CONTENT

InTouch

Double or Hybrid Diabetes[1]

➤ The World Health Organization (WHO) defines diabetes as a collection of metabolic disorders marked by persistent hyperglycemia, which can damage several organs, including the heart, kidneys, eyes, nerves, arteries, and ultimately lead to malfunction.

Two main types of diabetes

Type 1 diabetes (T1D)

- A young lean person with 90–100% of β-cell function loss
- Insulin treatment

Type 2 diabetes (T2D)

- An older, overweight, or obese person
- Insulin resistance (IR, functional failure of β-cells and insulin deficiency)
- Patients usually suffer from other diseases, especially cardiovascular diseases
- Oral antidiabetic drugs are needed at the beginning; whereas, insulin treatment is needed at a later point of time

Double diabetes (DD)

Hybrid diabetes, or type 1.5 diabetes, is generally described as the presence of the IR characteristic of metabolic syndrome in individuals diagnosed with T1D

ONE IN FOUR

patients suffering from T1D meet the criteria for metabolic syndrome (MS) and can be identified as an individual with DD

↓

Increases risk of micro and macroangiopathic complications (independent of glycemic control)

Insulin Resistance and Type 1 Diabetes—possible Explanations for this Association

Insulin resistance and type 1 diabetes coexist in a mechanism that is probably complex and not fully understood.

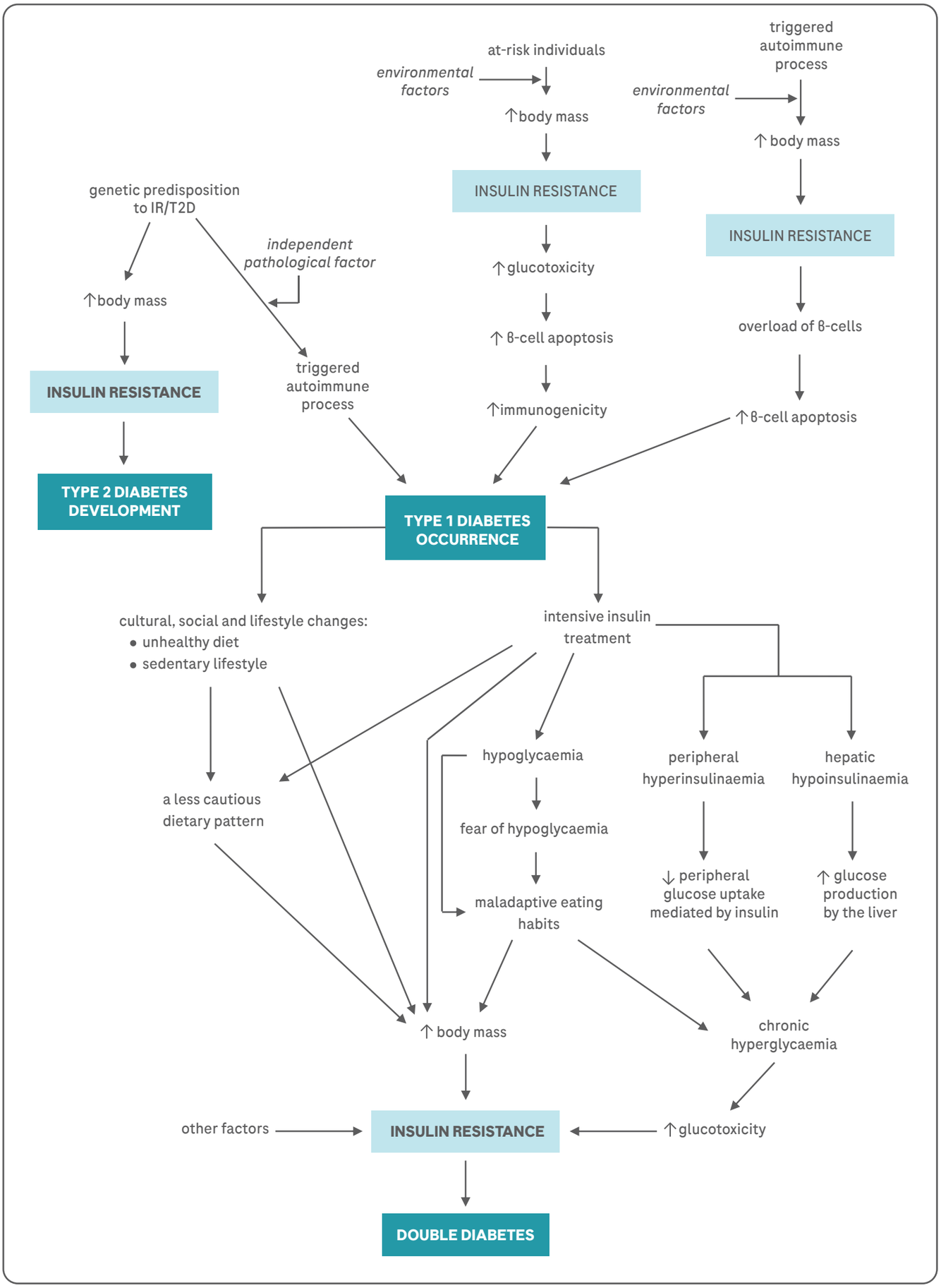


Figure 1: Pathophysiology of double diabetes

IR- insulin resistance; T2D- type 2 diabetes

Recognition of Double Diabetes—the role of Indirect Insulin Resistance Markers

Hyperinsulinaemic-euglycaemic clamp technique

- The gold standard
- Hyperinsulinaemic-euglycaemic clamp technique for calculating glucose disposal rate (GDR)
- Invasive, expensive, time-consuming and technically complicated

Homeostatic model assessment for insulin resistance (HOMA-IR)

- Used for routine assessment of insulin resistance
- Cannot be used in patients suffering from T1D

Estimated glucose disposal rate (eGDR)

- Indirect markers of insulin resistance
- Less than 8 was used in the classification criteria for double diabetes

Treatment in Double Diabetes

Metformin

- Decreases hepatic gluconeogenesis and increases peripheral glucose uptake stimulated by insulin through different pathways
- A reasonable choice for double-diabetic individuals because of its ability to reduce insulin resistance, beneficial cardiovascular influence and safety

Sodium-glucose co-transporter type 2 (SGLT-2) inhibitors

- Reduce reabsorption of filtered glucose in renal proximal tubules, which causes glycosuria and lowers glycemia
- One of the possible therapies for double diabetes, especially in individuals with excessive body weight and/or present cardiovascular risk factors

Glucagon-like peptide-1 receptor agonists (GLP1-RAs)

- Stimulate glucose-dependent insulin secretion, inhibit glucagon secretion from pancreatic α cells during hyperglycemia slows down gastric emptying and decreases appetite
- GLP1-RAs should be considered when a patient has excessive body weight

Lifestyle Changes

Diet

- An important modifiable risk factor for the development of insulin resistance in T1D
- High protein, low fat, and optimum carbohydrate intake with increased intake of dietary fiber may improve insulin sensitivity
- An isocaloric low-fat diet, may improve insulin sensitivity

Regular Physical Activity

- It reduces insulin resistance and daily dose of insulin without influencing HbA1c

Double diabetes is a serious clinical problem, as it is associated with a significantly increased risk of developing complications (especially macrovascular complications) and require additional interventions, such as lifestyle modification or the addition of metformin, SGLT-2 inhibitors or GLP-1RAs to insulin therapy.

Medical Management vs Bariatric Surgery in Type 2 Diabetes[2]

Study Objective

To determine long-term glycemic control and safety of bariatric surgery compared with medical/lifestyle management of type 2 diabetes

Study Design

Randomized control trial

Study Population

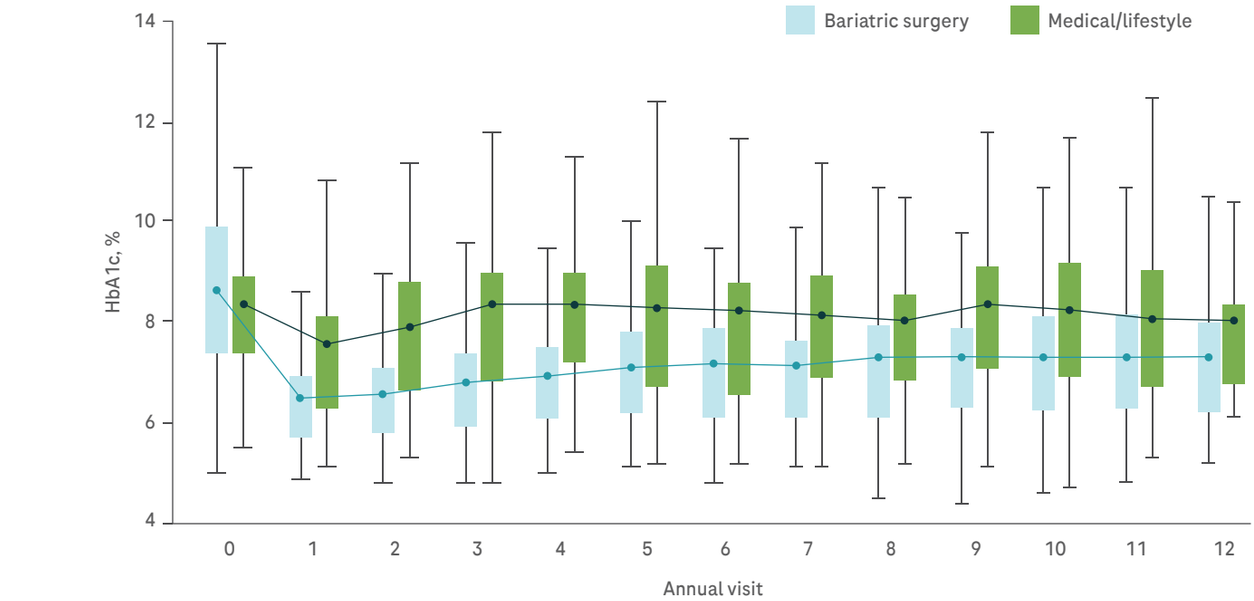
N= 316 individuals with type 2 diabetes who were randomized to undergo bariatric surgery vs medical/lifestyle intervention for management of type 2 diabetes

Study Outcomes

Changes in hemoglobin A1c (HbA1c) from baseline to 7 years for all participants.
Data reported for up to 12 years

Results:

- Despite higher baseline values, the bariatric surgery group had significantly lower HbA1c levels than the medical/lifestyle group at all points after baseline (P < .001) over 12 years.

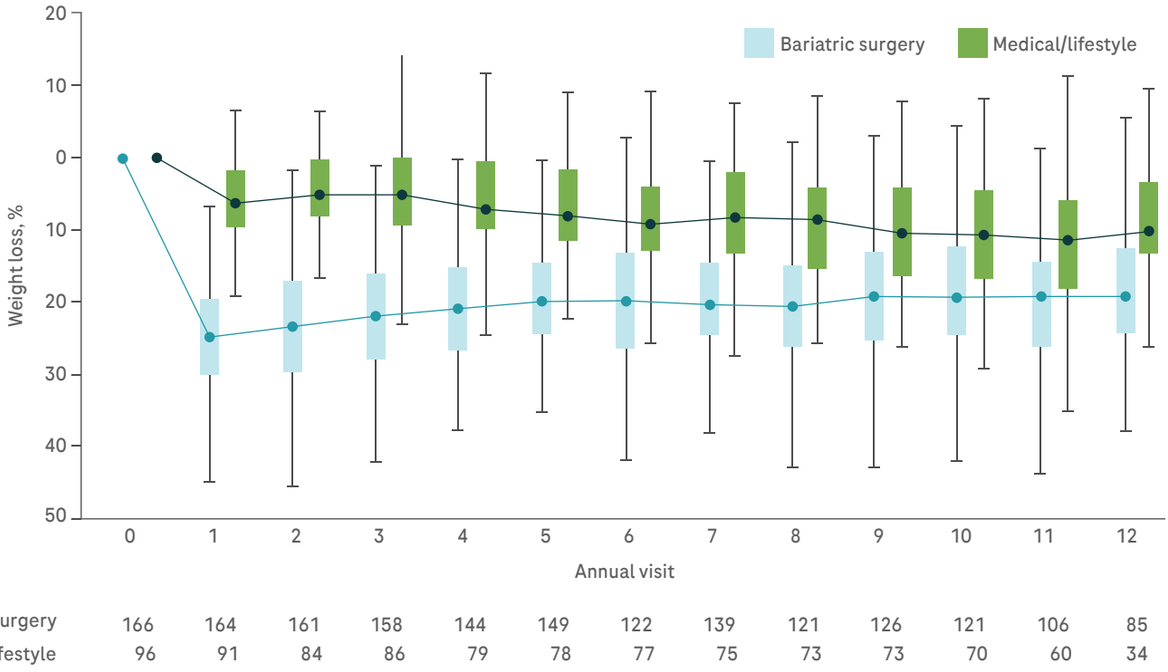


No. at risk													
Bariatric surgery	166	164	160	157	147	152	118	136	119	126	119	100	83
Medical/lifestyle	96	92	88	86	80	86	78	82	72	71	68	55	31

Figure 2: Hemoglobin A1c (HbA1c) by group
The lines and dots represent the least-square estimates obtained from the model and the boxplots represent the raw data. Horizontal lines within the boxes demonstrate median values, dots indicate mean values, the tops and bottoms of the boxes represent the IQR, and the whiskers represent the highest and lowest values within 1.5 × the IQR.
Adapted from: Courcoulas AP et al.

- Mean HbA1c decreased to 8.0% from a baseline of 8.2% (difference, 0.2%) in the medical/lifestyle group and from 8.7% to 7.2% (difference,1.6%) in the bariatric surgery group at 7 years.
- Following a 25% crossover from a medical/lifestyle intervention to a surgical intervention, a per-protocol sensitivity analysis revealed a change in mean HbA1c at 7 years of 0.1% for the medical/lifestyle group and −1.4% for the bariatric surgery group, with a between-group difference of −1.5%.
- About 0.5% of participants in the medical/lifestyle group achieved remission of diabetes at 1 year, compared with 50.8% in the bariatric surgery group.
- In the medical/lifestyle group, remission at year 7 was 6.2%, while in the bariatric surgery group, it was 18.2% (P =0.02). This difference was still statistically significant at year 12 (P <0.001).
- At 7 years, 26.7% of participants in the medical/lifestyle group had an HbA1c of less than 7.0%, compared with 54.1% of participants in the bariatric surgery group (P < 0.001).

- In the group undergoing bariatric surgery, better glycemic control was attained with fewer prescription drugs.
- Seven years following bariatric surgery, there was a statistically significant difference in weight loss: 8.3% in the medical/lifestyle group and 19.9% in the surgical group (P <0.001; Figure 3).



No. at risk													
Bariatric surgery	166	164	161	158	144	149	122	139	121	126	121	106	85
Medical/lifestyle	96	91	84	86	79	78	77	75	73	73	70	60	34

Figure 3: Weight loss

The lines and dots represent the least-square estimates obtained from the model and the boxplots represent the raw data. Horizontal lines within the boxes demonstrate median values, dots indicate mean values, the tops and bottoms of the boxes represent the IQR, and the whiskers represent the highest and lowest values within 1.5 × the IQR.
Adapted from: Courcoulas AP et al.

- At 7 years, a BMI less than or equal to 25 was achieved in 2.7% of participants in the medical/lifestyle group and 14.4% in the bariatric surgery group and at 12 years, these rates were 0% in the medical/lifestyle group and 15.3% in the bariatric surgery group.

When compared to medical and lifestyle interventions, bariatric surgery lead to better glycemic control, lower medication usage for diabetes, and higher rates of diabetes remission.

Bridge to Excellence

ADA-Standards of Care in Diabetes—2024[3]

Q 1. When should people with diabetes using CGM have access to BGM ?

A. Whenever there is suspicion that the CGM is inaccurate

B. When there is a disruption in CGM transmission

C. If calibration required or warning message appears in CGM

D. In any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min)

E. All of the Above

Q 2. Select the best answer- For glycemic control in patients with type 2 diabetes and atherosclerotic cardiovascular disease, ADA recommends the use of

A. SGLT-2 inhibitors

B. GLP-1RA

C. Any SGLT-2inhibitors/GLP-1RA

D. SGLT-2 inhibitors / GLP-1RAs with demonstrated cardiovascular benefits

Q 3. Ketoacidosis in type 2 diabetes usually arises in association with the stress of another illness.

A. True

B. False

Spotlight

Self-monitoring of Blood Glucose and Glycemic Control in Patients with Type 2 Diabetes[4]

- For patients with type 2 diabetes receiving insulin treatment, numerous international and regional guidelines strongly advise self-monitoring of blood glucose (SMBG), as it enhances glycemic control.
- It is still debatable if SMBG can help people with type 2 diabetes not receiving insulin therapy with their glycemic control.

Study Objective	To determine the association between the frequency of self-monitoring of blood glucose (SMBG) and glycemic control in patients with type 2 diabetes
Study Design	Retrospective study
Study Population	N= 3,630 patients with type 2 diabetes (n=2456 non-insulin-treated patients were divided into SMBG ≤ 6 times/week and > 6 times/week groups and n=1174 insulin-treated patients were divided into SMBG ≤ 9 times/week and > 9 times/week groups)
Study Outcomes	Changes in fasting blood glucose (FBG) and postprandial blood glucose (PBG) from baseline to 6 months

Results:

- After six months, a higher SMBG frequency was linked to a considerably larger magnitude of FBG and PBG reduction in non-insulin-treated patients than a lower SMBG frequency.
- In the SMBG ≤ 6 times/week group, the mean reduction in FBG from baseline to six months was 3.2 mg/dl, but in the SMBG > 6 times/week group, it was 10.6 mg/dl (P < 0.001).
- In the SMBG ≤ 6 times/week group, the mean reduction of PBG was 6.5 mg/dl, but in the SMBG > 6 times/week group, it was 16.4 mg/dl (P < 0.001).
- Among patients using insulin, the average decrease in FBG from baseline to six months was 7.0 mg/dl in the group with SMBG > nine times per week and 5.2 mg/dl in the group with SMBG ≤ nine times per week (P = 0.371).
- In the group with SMBG ≤ 9 times/week, the mean reduction in PBG was 6.7 mg/dl, but in the group with SMBG > 9 times/week, it was 11.5 mg/dl (P= 0.143).
- Patients in the SMBG > 6 times/week group had a greater FBG reduction than patients in the SMBG ≤ 6 times/week group, with a maximal difference of 10.6 mg/dl at 6 months and a minimum difference of 8.6 mg/dl at 12 months (Figure 4).

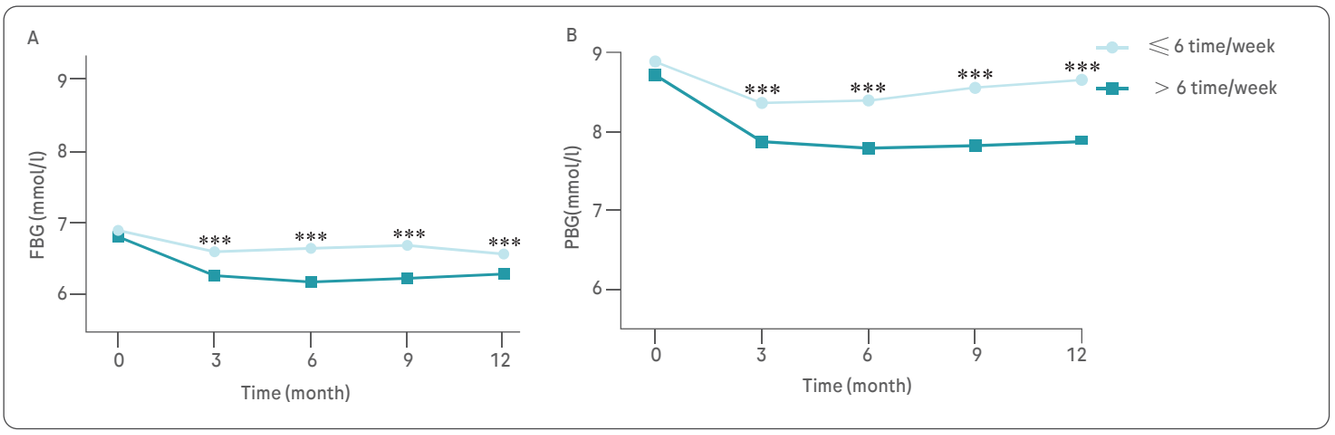


Figure 4: Longitudinal FBG and PBG trajectory at each time point during the follow-up period. Mean FBG levels of non-insulin-treated patients(A) at 3, 6, 9, and 12 months. Mean PBG levels of non-insulin-treated patients(B) at 3, 6, 9, and 12 months.

*** P < 0.001, ** P < 0.05. FBG, fasting blood glucose; PBG, postprandial blood glucose; FBG, PBG (in mmol/l, 1 mmol/L = 18 mg/dl)
Adapted from: Sun X et al.

- PBG reductions at 3, 9, and 12 months in patients with SMBG > 6 times/week were significantly higher than reductions observed in those with SMBG ≤ 6 times/week (14.9 vs. 8.6 mg/dl, P < 0.001; 15.8 vs. 5.6 mmol/l, P < 0.001; and 14.9 vs. 4.5 mg/dl, P < 0.001, respectively.

- In non-insulin-treated patients, those in the SMBG > 6 times/week group achieved a higher declining level of staple food calorie intake (-595.5 vs. - 370.6 kcal/day, P = 0.002); also, insulin-treated patients reported significant differences in the calorie intake through staple foods.

- Among patients receiving non-insulin therapy, patients with high SMBG frequency increased their physical activity, while patients with low monitoring frequency decreased their exercise (49.5 vs. - 5.8 MET-min, P < 0.001) and those with high SMBG frequency in insulin-treated patients also had increased exercise consumption (27.9 vs. - 4.9 MET-min, P = 0.012).

- In patients receiving non-insulin therapy, the ratio reflecting the frequency of changing hypoglycemic drugs was higher in patients monitoring > 6 times/week compared with the ≤ 6 times/week group (0.50 vs. 0.36, P < 0.001).

Patients with type 2 diabetes who are receiving oral medication can benefit from frequent SMBG, which also encourages dietary changes, hypoglycemic therapy, and physical activity.

Frequent SMBG was associated with better glycemic control in insulin-treated type 2 diabetes with poor glycemic control.

Patients with a higher SMBG frequency tended to reduce staple foods calorie intake, increase the amount of physical activity, and adjust their medication regardless of whether they received or did not receive insulin therapy

Diabetes Connect

The Effect of Diabetes Distress on Glycemic Control and its Complications[5]

According to a meta-analysis, up to 36% of people with type 2 diabetes mellitus (T2DM) experience diabetes distress.

Study Objective	To study the association between diabetes distress, glycemic control and diabetic complications and further investigate the clinical features in patients with high diabetes distress
Study Population	N= 1862 individuals with type 2 diabetes mellitus (T2DM) who completed diabetic complication studies and the Korean version of the Problem Areas in Diabetes Survey (PAID-K)

A PAID-K score ≥ 40 was defined as high distress.

Results:

- Higher PAID-K scores correlated with female genders, younger age, longer diabetes duration, higher HbA1c, HDL-C, LDL-C levels, lower total energy intake, higher carbohydrate intake and lower fiber intake in univariable analysis.
- As per the multivariable linear regression model, age ($p < 0.001$), female gender ($p = 0.006$), duration of diabetes ($p < 0.001$), and carbohydrate intake ($p = 0.006$) were independently associated with PAID-K scores after adjusting for the other co-variables.
- Albuminuria and diabetic neuropathy were more common in the high distress group (29.1% vs. 21.6%; $p = 0.010$, 31.2% vs. 20.4%; $p < 0.001$, respectively).
- The odds of diabetic neuropathy were higher in those who had significant levels of discomfort.
- There was no correlation seen between high levels of distress and carotid artery plaques, albuminuria, or diabetic retinopathy.
- High-distressed individuals showed greater baseline HbA1c levels than low-distressed ones. After three years of follow-up, the groups' differences remained the same.
- At baseline and three years into the follow-up, the percentage of patients with well-controlled diabetes, which is defined as having a HbA1c of less than 6.5%, was significantly lower in the high-distress group 19.4% (68/350) and 17.7% (62/350), compared to 29.4% (170/578) and 28.7% (166/578) in the low-distress group.
- When the individuals with HbA1c < 6.5% (at the time of survey) were analyzed separately it was observed that after 3 years of follow-up, only 41.2% (28 of 68) of patients in the high-distress group maintained a HbA1c level <6.5%, while 60.6% (103 of 170) of patients in the low-distress group maintained well-controlled diabetes.
- A separate analysis performed on individuals with a baseline HbA1c ≥ 6.5% (at the time of the survey) reported that after 3-years of follow-up the high-distress group consistently maintained significantly elevated HbA1c levels (all $p < 0.05$).

High levels of diabetes distress were linked to an increased risk of developing diabetic neuropathy and ongoing hyperglycemia, whereas it was not linked to albuminuria, carotid artery plaques, or diabetic retinopathy.

Diabetes in Control

The Role of Blood Glucose Monitoring in Diabetes Management[6]

Case History:

Mrs. Y has been a 50-year-old woman with type 2 diabetes for 11 years

BMI: 25 kg/m^2
Recent A1C: 8.5%
She has not been checking her glucose.

Current Medication:

- Metformin 1,000 mg twice daily and glipizide 10 mg before breakfast and dinner

Chief Complaint:

- She notes feeling tired most of the time.

What was Recommended?

- A 7-point profile for 3 days before her next clinic visit to get a better idea of her glucose levels throughout the day.

Mrs.Y's glycemic targets are 80–130 mg/dL before meals and <180 mg/dL 2 hrs after meals.							
	BB	AB	BL	AL	BD	AD	BT
Monday	125	201	150	256	129	259	203
Tuesday	130	249	174	241	122	263	214
Wednesday	129	223	142	203	126	281	199

Table: 3-Day, 7-Point Glucose Profile (mg/dL)

AB, after breakfast; AD, after dinner; AL, after lunch; BB, before breakfast; BD, before dinner; BL, before lunch; BT, bedtime

What Patterns Do You See?

- Mrs. Y.'s pre-breakfast values are all within her target range.
- However, her post-meal values are above range, as are those at bedtime.
- The only times during the day that she is in the target range are before breakfast and before dinner.
- Mrs. Y. takes a walk every day 3 hours after lunch, which lowers her pre-dinner glucose level into the target range.

What Patterns Do You See?

- Mrs. Y needs more medication to manage her post-meal glucose excursions.

Bridge to Excellence

Answers

1. **E. All of the Above**

As recommended by the device manufacturers and the U.S. Food and Drug Administration (FDA), people with diabetes using CGM must have access to BGM for multiple reasons, including whenever there is suspicion that the CGM is inaccurate, while waiting for warm-up, when there is a disruption in CGM transmission, for calibration (if needed) or if a warning message appears, when CGM supplies are delayed, and in any clinical setting where glucose levels are changing rapidly (>2 mg/dL/min), which could cause a discrepancy between CGM and blood glucose values.

2. **D**

SGLT-2 inhibitors / GLP-1RAs with demonstrated cardiovascular benefits

3. **A. True**

Stressful events (e.g., illness, trauma, and surgery) increase the risk of both hyperglycemia and hypoglycemia among individuals with diabetes. In severe cases, they may precipitate diabetic ketoacidosis or a nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care. Individuals with diabetes experiencing illness or other stressful events should be assessed for the need for more frequent monitoring of glucose; ketosis-prone individuals also require urine or blood ketone monitoring.

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