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**DIABETES & MET ABOLISM**

**JOURNAL**



Not Control but Conquest: Strategies for the Remission of Type 2 Diabetes Mellitus

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A durable normoglycemic state was observed in several studies that treated type 2 diabetes mellitus (T2DM) patients through metabolic surgery, intensive therapeutic intervention, or significant lifestyle modification, and it was confirmed that the function- al β-cell mass was also restored to a normal level. Therefore, expert consensus introduced the concept of remission as a common term to express this phenomenon in 2009. Throughout this article, we introduce the recently updated consensus statement on the remission of T2DM in 2021 and share our perspective on the remission of diabetes. There is a need for more research on remis- sion in Korea as well as in Western countries. Remission appears to be prompted by proactive treatment for hyperglycemia and significant weight loss prior to irreversible β-cell changes. T2DM is not a diagnosis for vulnerable individuals to helplessly accept. We attempt to explain how remission of T2DM can be achieved through a personalized approach. It may be necessary to change the concept of T2DM towards that of an urgent condition that requires rapid intervention rather than a chronic, progressive dis- ease. We must grasp this paradigm shift in our understanding of T2DM for the benefit of our patients as endocrine experts.

**Keywords:** Consensus; Diabetes mellitus, type 2; Recovery of function

# INTRODUCTION

Diabetes is classified into type 1 and type 2 according to classi- cal dichotomy. Unlike type 1 diabetes mellitus, which is the predominant cause of decreased insulin secretion due to pan- creatic damage related to autoimmunity, type 2 diabetes melli- tus (T2DM) has multiple causes, such as genetic and environ- mental factors [1]. Although genetic predisposition plays a role in the onset of T2DM, most cases develop after middle age, and associations with diet, lifestyle, and weight gain have been confirmed [2]. A progressive decline in -cell function is ob- served in most T2DM patients [3]. More drugs are required over time [4], and irreversible complications can arise [5].

However, normalization of blood glucose levels can be achieved and sustained without therapeutic intervention in some patients [6], and this semipermanent improvement of

diabetes is being observed more often with recently updated treatments [7,8]. A durable normoglycemic state was observed in a number of studies that treated T2DM patients through metabolic surgery, intensive therapeutic interventions or sig- nificant lifestyle modification [9-11]. It was confirmed that the functional -cell mass was also restored to a normal level [12].

Therefore, expert consensus introduced the concept of re- mission as a common term to express this phenomenon in 2009 [13]. Throughout this article, we introduce the recently updated consensus statement on the remission of T2DM in 2021 [14] and share our perspective on diabetes remission.

# CAN DIABETES BE CURED? DEFINITION OF REMISSION

Defining remission of T2DM is difficult. Unlike diseases that

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sometimes resolve completely and are classified as disease sta- tus versus healthy, diabetes is defined by hyperglycemia based on constantly changing blood glucose levels in the body that may be affected in the short term by temporary events such as drug effects, pregnancy, and acute illnesses [15-17].

Different expressions, such as cure, reversal, resolution, and remission, have been used in various studies to express “the oc- currence of durable normoglycemia without antidiabetic medi- cations,” which is confirmed after diabetes is diagnosed due to persistent hyperglycemia [18-20]. Therefore, a group of experts proposed expressing the state of postdiabetes as “remission” through a consensus meeting in 2009. In a consensus statement for 2021, the group explained that remission was adopted as a representative term to express the normalization of glycemic control according to the opinion that it can reflect the charac- teristics of susceptible individuals who may require continuous monitoring and support. The definitions and criteria for diabet- ic remission defined in 2009 and 2021 are presented in Table 1.

In the initial consensus from 2009, partial remission and complete remission were diagnosed for prediabetes and nor- mal blood glucose levels, respectively, and criteria subdivided into prolonged remission were presented when complete re- mission status was more than 5 years [13]. However, in the new consensus from 2021, remission was changed to a single diagnostic standard, and the classification of the period was re- moved considering the complexity and lack of evidence for the standards of blood glucose level and maintenance period [14].

As a diagnostic criterion, it was recommended to measure the glycosylated hemoglobin (HbA1c) level 3 months after the discontinuation of drug treatment [21], and remission was confirmed if the HbA1c level was found to be less than 6.5%.

In clinical situations where HbA1c may not reflect blood glu- cose levels, fasting glucose or the 2-hour postprandial glucose of oral glucose tolerance test (OGTT) can be used according to the diagnostic criteria for diabetes, but OGTT was described as an undesirable method due to the variability and complexity of the test. Since continuous glucose monitoring (CGM) has been recently applied, it is recommended to use the estimated HbA1c level (eA1c) or a glucose management indicator on CGM [22].

This suggested definition is primarily based on expert opin- ion, and there is not much evidence on the frequency, durabili- ty, and long-term medical outcome of remission status. In par- ticular, it is worth noting that remission does not mean com- plete resolution of diabetes, as the definition of diabetic remis- sion includes temporary remission of hyperglycemia over sev- eral months. The remission of T2DM is an unknown field that requires continued attention.

# STRATEGIES FOR THE REMISSION OF TYPE 2 DIABETES MELLITUS

The number of patients reaching remission was extremely low in the natural course of diabetes. In a cohort study of 25.6 mil- lion American adults who received standard medical therapy, 1.5% of patients reported normal glycemic control that could stop treatment, and prolonged normalization over 5 years was 0.007% [6]. However, it has been consistently reported that more than half of patients can achieve remission with recent treatment methods that induce active glycemic control and significant weight loss (Tables 2-4). New diabetes drugs with significant weight loss effects have recently been developed

**Table 1.** Remission of type 2 diabetes mellitus as defined by the consensus expert groups from the United States and Europe

|  |  |
| --- | --- |
| 2009 [13] | 2021 [14] |
| Partial remission  Hyperglycemia below diagnostic thresholds for diabetes At least 1 year’s duration  No active pharmacologic therapy or ongoing procedures Complete remission  Normal glycemic measures At least 1 year’s duration  No active pharmacologic therapy or ongoing procedures Prolonged remission  Complete remission of at least 5 years’ duration | Remission  A return of glycosylated hemoglobin to <6.5%  (<48 mmol/mol) that occurs spontaneously or following an intervention and that persists for at least 3 months  Alternative criteria  Fasting plasma glucose <126 mg/dL (<7.0 mmol/L)  Estimated glycosylated hemoglobin <6.5% calculated from continuous glucose monitoring values |

Adapted from Buse et al. [13], and Riddle et al. [14], with permission from Oxford University Press.

and are expected to help patients achieve remission of T2DM [23,24].

**Metabolic surgery for patients with morbid obesity** Surgical intervention increases satiety and decreases absorp- tion by physically narrowing the path through which ingested food passes. In addition to weight loss, this method is accom- panied by favorable effects on glycemic control including the

threshold increment of incretin hormones caused by changes in intestinal structure [25,26]. Metabolic surgery has various forms, such as adjustable gastric band, vertical sleeve gastrec- tomy, and Roux-en-Y gastric bypass (RYGB). The effect may be different depending on the surgical method [27-29]. Dia- betic remission was associated with postoperative weight loss, but subjects receiving RYGB were twice as likely to have diabe- tes remission than laparoscopic adjustable gastric banding

**Table 2.** Remission rates of T2DM after metabolic surgery confirmed by randomized clinical trials

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Patients | Type | Number | Follow- up, yr | Weight-loss | End-point | Outcome |
| Dixon et al. [31] | T2DM within 2 years BMI 30–40 kg/m2 | AGB vs. conventional therapy | 30 vs. 30 | 2 | 20.7% vs. 1.4% | HbA1c <6.2% | 73% vs. 13% |
| Ding et al. [32] | T2DM  BMI 30–45 kg/m2 | AGB vs. ILMI | 23 vs. 22 | 1 | 13.5 kg vs. 8.5 kg | HbA1c <6.5%a | 33% vs. 23% |
| Courcoulas et al. [33] | T2DM  BMI 30–40 kg/m2 | RYGB vs. AGB vs. ILMI | 21 vs. 20  vs. 20 | 1 | 27.0% vs. 17.3%  vs. 10.2% | HbA1c <5.7% | 27% vs. 23%  vs. 0% |
| Schauer et al. [34] | T2DM  BMI 27–43 kg/m2 | RYGB vs. SG vs. ILMI | 50 vs. 50  vs. 50 | 1 | 29.4 kg vs. 25.1 kg vs. 5.4 kg | HbA1c <6.0% | 42% vs. 37%  vs. 12% |
| Ikramuddin et al. [35] | T2DM  BMI 30–40 kg/m2 | RYGB vs. ILMI | 60 vs. 60 | 1 | 26.1% vs. 7.9% | HbA1c <7.0% | 49% vs. 19% |
| Halperin et al. [36] | T2DM within 1 year BMI 30–42 kg/m2 | RYGB vs. ILMI | 19 vs. 19 | 1 | 5.1 kg vs. 1.4 kg | HbA1c <6.5% | 58% vs. 16% |
| Cummings et al. [37] | T2DM  BMI 30–45 kg/m2 | RYGB vs. ILMI | 23 vs. 20 | 1 | 25.8% vs. 6.4% | HbA1c <6.0% | 60% vs. 6% |
| Mingrone et al. [38] | T2DM over 5 years BMI over 35 kg/m2 | BPD vs. RYGB vs. ILMI | 20 vs. 20  vs. 20 | 2 | 33.8% vs. 33.3%  vs. 4.7% | HbA1c <6.5% | 95% vs. 75%  vs. 0% |

T2DM, type 2 diabetes mellitus; BMI, body mass index; AGB, adjustable gastric band; HbA1c, glycosylated hemoglobin; ILMI, intensive life- style and medical intervention; RYGB, Roun-en-Y gastric bypass; SG, sleeve gastrectomy; BPD, bilopancreatic diversion.

aOn or off medication.

**Table 3.** Remission rates of T2DM after intensive insulin therapy in newly diagnosed patients as confirmed by randomized clini- cal trials

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Patients | Type | Number | Follow-up | End-point | Outcome |
| Ilkova et al. [50] | Newly diagnosed T2DM | CSII for 2 weeks | 13 | 6 months | FPG <7.8 mmol/L or PPG <10.0 mmol/L | 69% |
| Li et al. [51] | Newly diagnosed T2DM | CSII for 2 weeks | 138 | 2-year | FPG <7.0 mmol/L or PPG <10.0 mmol/L | 42% |
| Weng et al. [52] | Newly diagnosed T2DM | CSII vs. MDI vs. OHA for 2 weeks | 124 vs. 113 vs. 94 | 1-year | FPG <6.1 mmol/L or PPG < 8.0 mmol/L | 51% vs. 45% vs. 27% |
| Chen et al. [53] | Newly diagnosed T2DM | CSII for 2 weeks | 118 | 1-year | FPG <7.0 mmol/L or PPG <10.0 mmol/L | 55% |
| Chon et al. [54] | Newly diagnosed T2DM | MDI vs. OHA for 12 weeks | 50 vs. 47 | 2-year | HbA1c <7% | 47% vs. 23% |

T2DM, type 2 diabetes mellitus; CSII, continuous subcutaneous insulin infusion; FPG, fasting plasma glucose; PPG, postprandial plasma glu- cose; MDI, multiple daily insulin injection; OHA, oral hypoglycemic agent; HbA1c, glycosylated hemoglobin.

**Table 4.** Remission rates of T2DM after a very-low-calorie diet in newly diagnosed patients as confirmed by randomized clinical trials

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Patients | Type | Number | Follow-up | Weight-loss | End-point | Outcome |
| Lim et al. [76] | T2DM within 4 years BMI 25–45 kg/m2 | VLCD vs. ILMI  for 8 weeks | 11 vs. 8 | 2 months | 13.1 kg | FPG <126 mg/dL | 100% |
| Steven et al. [77] | T2DM within 4 years vs. T2DM over 8 years BMI 27–45 kg/m2 | VLCD for 8 weeks | 15 vs. 14 | 2 months | 14.5 kg vs. 13.9 kg | HbA1c <6.5% | 87% vs. 50% |
| Lean et al. [78] | T2DM within 6 years BMI 27–45 kg/m2 | VLCD vs. ILMI  for 3–5 months | 149 vs. 149 | 1 year | 10 kg vs. 1 kg | HbA1c <6.5% | 46% vs. 4% |
| Taheri et al. [79] | T2DM within 5 years BMI more than 27 kg/m2 | VLCD vs. ILMI  for 12 weeks | 70 vs. 70 | 1 year | 12 kg vs. 4 kg | HbA1c <6.5% | 61% vs. 12% |

T2DM, type 2 diabetes mellitus; BMI, body mass index; VLCD, very low-calorie diet; ILMI, intensive lifestyle and medical intervention; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin.

1.0

Modeled probability of remission

0.8

0.6

0.4

0.2

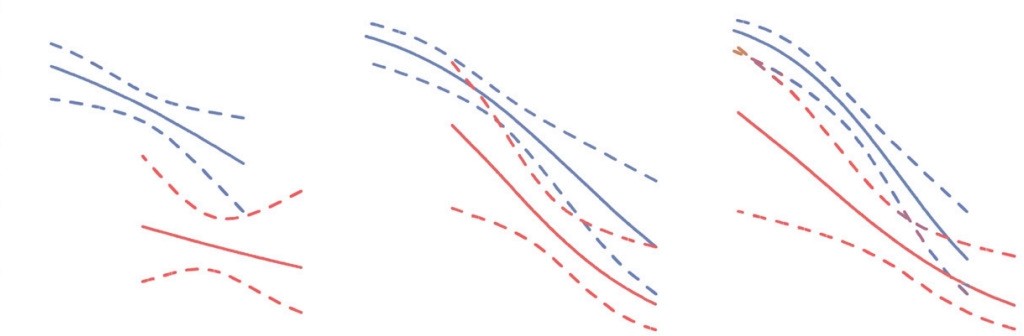
0

Year 1

Year 2

Year 3

−60 −40 −20 0 −60 −40 −20 0 −60 −40 −20 0



aRR, 1.91 (95% CI, 1.37−2.66)

aRR, 1.72 (95% CI, 1.26−2.35)

aRR, 1.92 (95% CI, 1.35−2.75)

Percent weight change

**Fig. 1.** Modeled probabilities for diabetes remission according to weight loss in patients who underwent laparoscopic adjustable gastric banding (red lines), and Roux-en-Y gastric bypass (blue lines). Adjusted relative risk (aRR) estimates and 95% confidence intervals were adjusted for percent weight change and a propensity score based on baseline demographic and clinical variables as- sociated with the type of surgery. Adapted from Purnell et al. [28], with permission from Oxford University Press.

(LAGB) even after adjusting for weight change (Fig. 1).

The first rationale for remission was presented through met- abolic, or bariatric surgery [30], and has been confirmed in a number of randomized clinical trials (Table 2) [31-38]. In a previous meta-analysis of 4,070 patients that included 19 ob- servational studies for metabolic surgery, the overall T2DM re- mission rate after the surgery reached 78% [39]. In addition, a meta-analysis of clinical trials showed that bariatric surgery had better outcomes than the nonsurgical option. The effec- tiveness of surgical intervention is quick and definite [40]. However, permanent structural changes did not guarantee eternal effects. In some patients, weight regain occurred, and the improvement glycemic control may worsen again [41]. Ad-

ditionally, surgical intervention is an invasive procedure that includes general anesthesia and can result in acute complica- tions, including death [42]. Chronic complications, such as malnutrition and mental illness, are also commonly observed [43-45].

Therefore, experts recommend selective surgical treatment for patients with morbid obesity that cannot be easily controlled with routine pharmacologic approaches or patients with severe obesity with a body mass index higher than 30 to 35 kg/m2 [46,47]. Significant weight loss is necessary for fat loss of the visceral organs in terms of diabetes remission [48], and meta- bolic surgery may be an effective method that can induce suffi- cient and reliable weight loss for severely obese patients.

100

Percentage of patients in remission

80

70

60

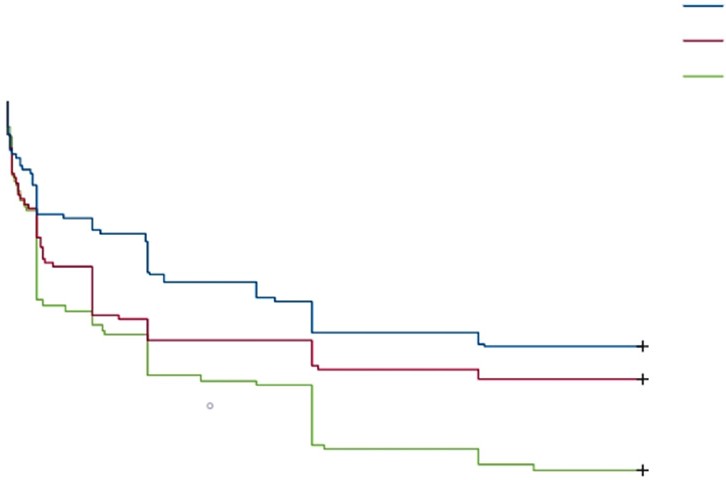
40

20

0

Number at risk

90 180 270 360 450



CSII MDI OHA

*P*=0.0012

Days in remission

lished that the amount of time spent in hyperglycemic condi- tions increases the risk of complications [60-62]. Therefore, proactive treatment intensification has been proposed to mini- mize the cumulative effect of hyperglycemia. Since the patho- genesis of T2DM is complex, a synergistic effect between sev- eral drugs can be expected by using a combination therapy of drugs with various mechanisms. Early combined therapy can prevent delays in glycemic control due to clinical inertia that occurs during sequential intensification. The use of early com- bination therapy may be superior to reach optimal glycemic control quickly [63,64]. The significant impact of combination therapy in restoring -cell function is receiving more attention with the development of new drugs [65].

However, indiscreet use of the initial intensive treatment

CSII 133 95 79 71 67

MDI 118 66 61 54 52

OHA 101 53 43 30 26

**Fig. 2.** Effect of intensive insulin therapy for 2 weeks at initial rapid correction of hyperglycemia on diabetic remission at 1 year after the intervention in patients with newly diagnosed type 2 diabetes mellitus. Adapted from Weng et al. [52], with permission from Elsevier. CSII, continuous subcutaneous in- sulin infusion; MDI, multiple daily insulin injection; OHA, oral hypoglycemic agent.

## Intensive insulin therapy for newly diagnosed patients with severe hyperglycemia

Remission was observed in newly diagnosed patients with uncontrolled hyperglycemia following 2 to 3 weeks of inten- sive insulin therapy [49]. In subsequent studies, randomized clinical trials were performed to compare conventional treat- ment and different insulin treatment methods, and status was evaluated to determine whether remission was reached (Table 3, Fig. 2) [50-54]. Remission following intensive insulin thera- py has been demonstrated to last more than 2 years, and it is believed that the shorter the time interval between diagnosis and intensive insulin therapy is, the greater the likelihood of remission [10]. -cell conservation was also confirmed after intensive treatment early in the disease process [55,56]. Long- term effectiveness of glycemic control was observed in pa- tients who received early combination therapy [57]. Improve- ment in -cell function and long-term -cell preservation was observed in patients treated with short-term intensive insulin therapy [58]. Therefore, early intervention for newly diag- nosed T2DM patients is considered one of the strategies.

The detrimental effects of hyperglycemia itself on -cell function and insulin action are known [59], and it is estab-

may result in overtreatment of patients with borderline blood glucose levels, who may have otherwise maintained adequate glycemic control with lifestyle modifications or monotherapy. Combination therapy is expensive [66], and may increase the likelihood of side effects from taking multiple drugs [67]. El- derly patients may require a minimal approach, considering the correlation between hypoglycemia risk and life expectancy. Therefore, a personalized approach is needed because sequen- tial approaches starting with minimal agents could be effective in some patients [68,69].

## Intensive weight management with dietary calorie- restriction

As a basic method to improve blood glucose control and re- duce pancreatic -cell burden, a lifestyle that reduces calorie intake and increases physical activity is recommended for all diabetic patients [70]. Among lifestyle modification strategies, the favorable effect of caloric restriction on glycemic control could be the most effective strategy in terms of both weight control and glycemic control [71-73]. In the meta-analysis of various weight loss methods, the very-low-calorie diet (VLCD) showed the most significant weight loss effect (Fig. 3).

VLCD refers to a diet that contains 800 kcal or less per day with a relatively high protein-to-calorie ratio and with essential micronutrients. This diet is usually served in liquid form for 3 to 4 months [74]. Researchers considered the VLCD protocol as a therapeutic approach for obese diabetic patients [75]. Re- cent studies have also evaluated diabetes remission in these pa- tients (Table 4) [76-79]. Lean et al. [78] combined VLCD with routine primary care and confirmed remission in 46% of study subjects. In the study subject group, the greater the weight loss

2

0

−2

−4

−6

Weight loss (kg)

−8

−10

−12

−14

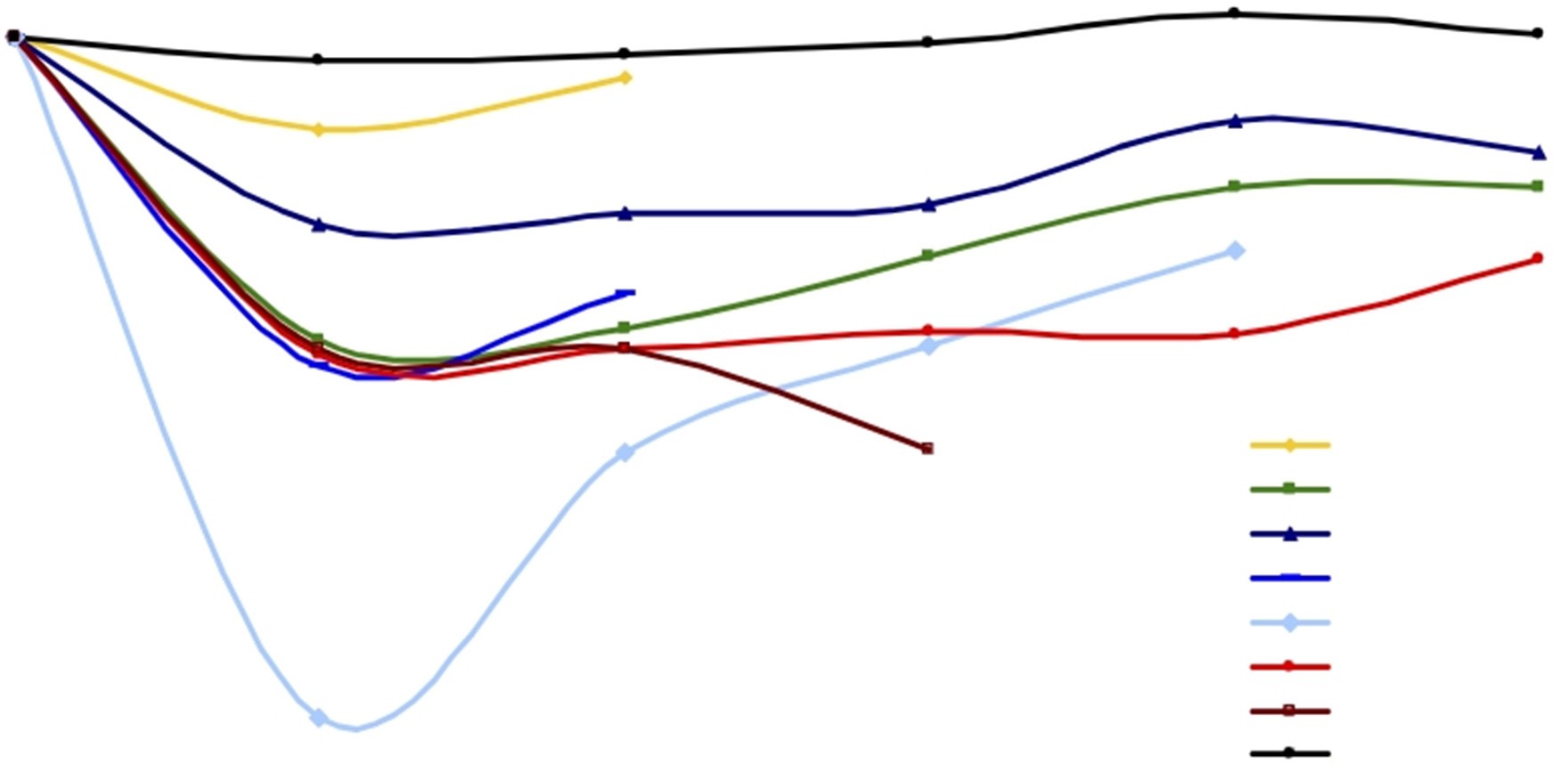
−16

−18

−20

Exercise alone Diet+exercise Diet alone

Meal replacements Very-low-energy diet Orlistat



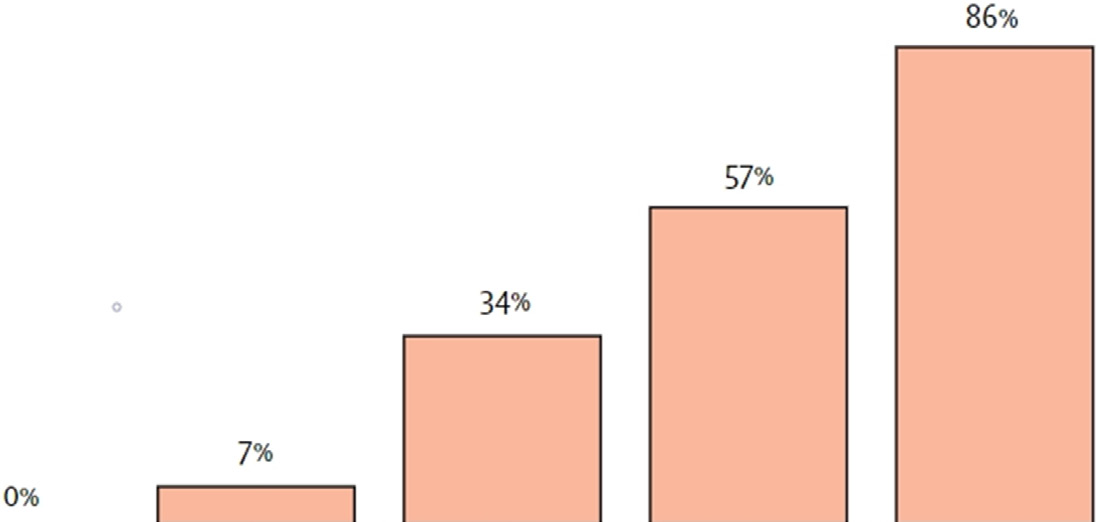
Sibutramine Advice alone

6 12 24 36 48

Month

**Fig. 3.** Average weight change of participants completing at least a 1-year intervention, consisting of a review of 80 studies. Adapt- ed from Franz et al. [72], with permission from Elsevier.

100



Odds ratio per kg weight loss 1.32; 95% CI, 1.23−1.41

*P*<0.0001

Proportion achieving remission at 12 months (%)

80

60

40

20

0

0 <5 5−10 10−15 ≥15

Weight loss at 12 months (kg)

**Fig. 4.** Proportion achieving remission at 12 months according to weight loss via a very-low-calorie diet for 3 to 5 months. Adapt- ed from Lean et al. [78], with permission from Elsevier. CI, confidence interval.

was, the higher the remission rate, which is shown in Fig. 4. Although VLCD is generally a safe method, it is recom-

mended that it be performed under medical supervision. Fa- tigue and gastrointestinal disturbances may occur in the early stages [80,81], and sudden death with arrhythmia has been re- ported, although it is rare [82]. Currently, VLCD is not recom- mended for individuals with normal weight [83]. Previous re- searchers have suggested that preoperative VLCD application to patients with severe obesity planning metabolic surgery can reduce perioperative complications and maximize the effec- tiveness of surgery [84].

**Development and clinical applications of new drugs** Recently, developed diabetes drugs have a unique mechanism, causing significant weight loss. For instance, sodium-glucose cotransporter-2 (SGLT2) inhibitors act on the proximal convo- luted tubule of the kidney to decrease glucose resorption in a way that induces glycosuria, and they have a glucose-lowering effect regardless of insulin secretion or insulin sensitivity [85]. This class of drugs can reduce weight and visceral fat because it is associated with urinary glucose excretion that causes caloric loss [86]. In a clinical trial using SGLT2 inhibitors in addition to basal insulin and metformin as an intensive intervention, the intervention group with SGLT2 inhibitors achieved more re-

mission than compared to the conventional group (24.7% vs. 16.9%), and reduced the risk of diabetes recurrence by 43% [23]. Glucagon-like peptide-1 (GLP1) is a type of incretin hormone that acts in the intestines and inhibits glucagon secretion; vari- ous types of GLP1 receptor agonists (GLP1-RAs) have been developed and used [87]. Liraglutide, a type of GLP1-RA, has been studied to help preserve pancreatic -cell function when used in early T2DM [88]. Recently, tirzepatide with higher po- tency has been developed and approved; it is a drug that exhib- its dual action in both types of incretins, glucose-dependent insulinotropic polypeptide (GIP) and GLP1 [89]. The drug re- sulted in a remission rate of 66% to 81%, depending on the drug dose over 52 weeks of use in a clinical study [90]. These drugs can produce rare hypoglycemic events and a large weight loss effect [91,92]. Therefore, we may consider these new med- ications rather than aggressive methods with known medical risks such as surgery, early intensive insulin therapy, and VLCD. However, as these drugs are relatively new methods, clear evidence for diabetes remission is lacking. Further studies

are needed on the effects of new drugs on diabetes remission.

In addition, these newly developed drugs are unavailable for a small number of patients. SGLT2 inhibitors cannot be used for patients with chronic kidney disease, and it has been report- ed that they may cause ketoacidosis in more patients than con- ventional drugs [93]. Since GLP1-RAs and tirzepatide are injec- tions, a psychological burden of patients is expected, and side effects such as local reactions at the injection site have been re- ported. Some patients discontinued the use of the drug due to gastrointestinal symptoms [94]. Moreover, these new drugs are expensive. Therefore, an approach that selects patients who may particularly benefit from this intervention may be necessary.

# HOW DOES DIABETES REMISSION OCCUR? PATHOPHYSIOLOGY FOR DIABETES REMISSION

## Dedifferentiation as a mechanism for degenerative changes in insulin-secreting β-cells

Predispositions that make individuals more susceptible to dia- betes include genetic factors [95], the nutritional status of the prenatal period [96], and the environment in the early years of life [97]. -Cells proliferate and secrete more insulin to adapt to the body’s increasing insulin requirements depending on the degree of weight gain [98]. However, -cell failure eventu- ally shows a progressive deterioration in which the drug de-

mand gradually increases because of chronic hyperglycemia and overload related to weight gain [99]. Previously, it was ex- plained that -cells undergo apoptosis and progressively die in the worsening course of diabetes. However, as the concept of dedifferentiation is proposed and studies to support it are pre- sented, it will become the basis for strategies to revitalize

-cells and restore function [100,101].

## Hypothesis of type 2 diabetes mellitus as an intestinal disease

Rubino, a surgeon who specializes in metabolic surgery, de- scribes diabetes as an operable intestinal disease, and he has paid attention to the improvement of diabetes and its mecha- nism after bariatric surgery [102]. Glycemic control improves rapidly within days of bariatric surgery, which occurs too quickly to account for weight loss alone [103]. Therefore, the structural change in the intestine was suggested as a mecha- nism for the improvement of blood glucose control. The change caused by food bypassing the proximal part of the small intestine is called the foregut hypothesis, and the change caused by food rapidly reaching the distal end of the small in- testine is called the hindgut hypothesis [104]. The intestinal hormone—incretins play a major role in these changes, and the enteroinsular axis was first proposed in 1969 by Unger and Eisentraut [105] as a mechanism for the association between diabetes and intestinal hormones. They studied gut hormones secreted from intestines that are stimulated by food, particu- larly by carbohydrates and affect insulin secretion [106]. As a significant hormone associated with diabetes, in particular, GLP1 and GIP are two incretins thought to have a significant effect. Agonists for these hormones have also been developed as diabetes drugs and have shown significant effects, and re- mission studies for these drugs need to be continued.

## Twin cycle hypothesis and personal fat threshold

Weight loss and consequent visceral fat loss are key for the re- mission of diabetes [107]. Some researchers have focused on the pathological role of fatty liver in T2DM in terms of energy balance and metabolic disturbances [108,109]. Fatty liver dis- ease is caused by the storage of extra fat and improves in the early stage of weight loss [110]. Fat reduction according to weight loss varies depending on the body part, and it was re- ported that 16% of weight loss was accompanied by a 30% in- tra-abdominal fat reduction and 65% intrahepatic triglyceride loss [111,112]. In 2008, Taylor [20] proposed the twin cycle hy-

pothesis, which posits that T2DM occurs because of a vicious cycle of fat accumulation in the liver and pancreas. Chronic ex- cess energy causes fatty liver and an increase in lipids in sys- temic circulation if the liver overflows with fat. Fatty liver re- duces insulin production and sensitivity and thus leads to a vi- cious cycle [113]. Finally, fat accumulates in the pancreas, lead- ing to decreased -cell function. He also proposed the concept of a personal fat threshold to explain the development of dia- betes in individuals with relatively low body weight, which is supported by genetic studies associated with the capacity for subcutaneous fat storage [114,115]. Even in prediabetic pa- tients who are of normal weight or slightly overweight who are not obese, weight loss may be helpful to prevent diabetes, which supports the personal fat threshold hypothesis [116].

# TIME IS OUTCOME? PREDICTORS OF DIABETES REMISSION

Because the induction of remission results in relatively drastic changes in the body, selecting the target group and timing of intervention can be crucial points of discussion. Since some individuals have reached remission status after metabolic sur- gery, an assessment tool has been developed to predict the out- comes of these patients before surgery, and these models are primarily based on whether -cell function is conserved (c- peptide), the degree to control of diabetes (HbA1c), the severi- ty of diabetes (number of antidiabetic drugs and insulin use), and the duration of diabetes [117-122]. To increase the predic- tive power, a method that considers the demographics, surgical methods, and comorbidities has also been proposed [123], and recently, attempts have been made to make predictions easier through biochemical biomarkers [124].

In studies based on metabolic surgery and VLCD, it was re- ported that younger patients were more likely to reach remis- sion [125]. In addition, the study that enrolled younger pa- tients [77] reported higher remission rates (remission rate at 1 year: 61% vs. 46%) than the study [78] involving relatively old- er patients (average age of study subjects: 41.9 years vs. 52.9 years). However, in a cohort study in which patients received conventional medical therapy, remission was reported to have a higher prevalence in elderly patients. The remission in the to- tal population was 1.5% [6], whereas the remission in the study targeting the population over 65 years old was 5% [126]. Al- though weight-based intervention appears to be more effective for patients at a younger age, diabetes in older adults may be

more likely to “disappear” in terms of genetic susceptibility and exposure to drugs that can cause diabetes.

If diabetes is present for a long period of time, patients’ met- abolic profiles are less likely to respond to weight changes [125]. The duration of diabetes was an important predictor of remission, which has been consistently reported in several studies [6,117,119,122,127,128]. Most patients treated with multiple antidiabetic drugs could not achieve remission even after significant weight loss following bariatric surgery due to irreversible -cell damage [129]. In particular, insulin treat- ment appears to be significant in relation to the severity of dia- betes and the degree of preservation of -cell function [6,118, 120-122].

In summary, factors such as the degree of glycemic control, whether insulin is needed and disease characteristics such as the duration of illness are considered to be significant factors rather than patient factors such as the patient’s age, sex, or BMI. In particular, the most important factor to reach remission may be early intervention for newly diagnosed diabetic patients. As with all diseases, early screening and active early treatment are thought to help improve the prognosis for diabetes.

# DOES DIABETES REMISSION PERSIST? THE STORY AFTER REMISSION

Individuals who have previously been diagnosed with diabetes are more susceptible to diabetes than other individuals and have a higher risk of relapse. Researchers believe that weight loss and maintenance are key to maintaining remission of T2DM [115,130]. Sometimes the body resists changes follow- ing significant weight loss, and weight is easily regained [131]. To form and maintain a healthy lifestyle and to maintain long- term remission of diabetes, the patient’s own will is important, but the cooperation and support of family members, partners, acquaintances, and members of society is essential [132].

In addition, hyperglycemia appears to continue to affect the body even after it has improved, as the long-term consequenc- es for hyperglycemic conditions, are referred to as the “meta- bolic memory” or “legacy effect” [133]. This effect is mainly as- sociated with microvascular complications rather than effects on macrovascular complications or survival [134]. It is thought that individuals liberated from hyperglycemia will require con- tinuous surveillance for recurrence and complications even af- ter remission is confirmed.

# UNMET NEEDS

## Validation of remission definitions

The current definition of remission was determined by expert opinion based on the diagnostic criteria for diabetes, and new criteria (including the duration of maintaining remission) or different glucose standards may have to be considered. It may be necessary to lower the cutoff to reduce the risk of recur- rence. The consensus of 2021 states that CGM-derived data can be used, but only the eA1c level is presented among the values. The data could be considered a novel metric, such as time in range (TIR), in the evaluation of remission.

## Postdiabetes surveillance

The consensus recommends that patients with a history of dia- betes after remission should undergo testing for glycemic sta- tus and complications related to diabetes at 1-year intervals. This is based on reported metabolic memory that is the lasting effect of previous hyperglycemic status despite improved gly- cemic control [135,136]. Through study of the long-term med- ical outcomes of patients following remission, how the moni- toring cycle should be carried out and which procedures should be used to check for complications can be the subject of additional discussion.

## Social intervention

With regard to the increase in the incidence of T2DM along with the prevalence of obesity, obesity may be not only a per-

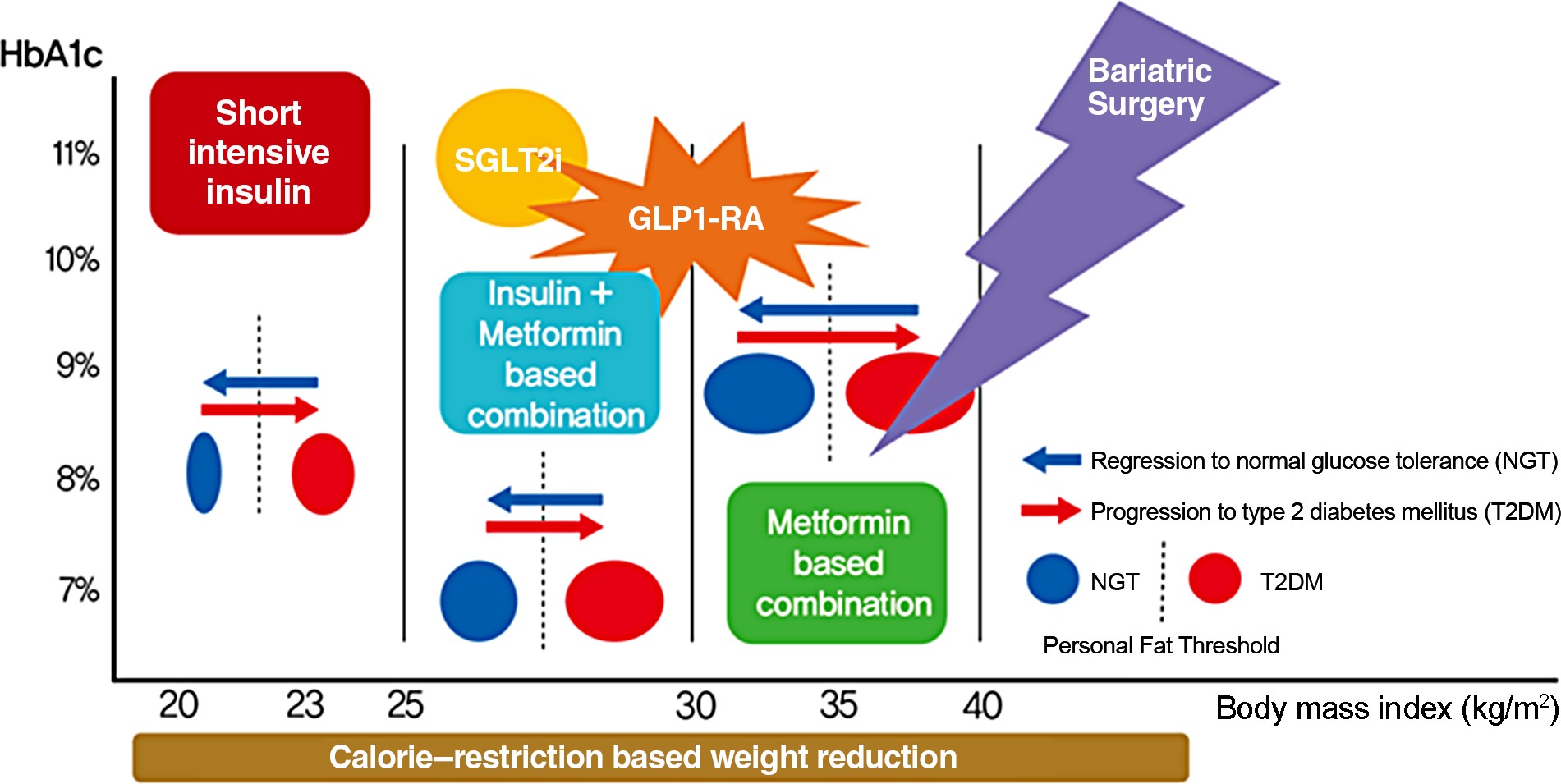
sonal problem but also a social burden [137]. Therefore, obesi- ty and related diseases are clearly fields that require interven- tion from the perspective of public health [138]. From the viewpoint of reducing the incidence of diabetes and the bur- den of medical expenses, the chronic disease management model for diabetes needs to be changed to a social intervention model for obesity [112], such as one that includes health cam- paigns for the general population and sugar taxes on food [139,140].

## Studies for Korean ethnicity

T2DM occurs at an earlier age in Asian populations than in other races. The Asian population shows reduced insulin se- cretion, low weight tendencies, and many complications [141]. In terms of remission evaluation according to each treatment method, there are relatively few studies conducted in the Asian population, especially for Koreans. Therefore, there is a need for more research on remission in Korea as well as in Western countries.

# CONCLUSIONS

Remission appears to be induced by intensive glycemic control and significant lifestyle change prior to irreversible -cell changes [142,143]. By implementing short-term intensive insu- lin therapy in patients with uncontrolled hyperglycemia at an early stage of the disease, -cell function improves, and remis- sion of T2DM can be secured for a considerable period. In pa-



**Fig. 5.** Summary of strategies for type 2 diabetes mellitus remission. HbA1c, glycosylated hemoglobin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; GLP1-RA, glucagon-like peptide-1 receptor agonist. Adapted from Taylor et al. [114], with permission from Portland Press.

tients who are overweight at the initial stage of diagnosis, remis- sion can be reached in more than half of patients if significant weight loss is induced by methods such as metabolic surgery or VLCD. New drugs, such SGLT2 inhibitors and GLP1-RAs, have a weight loss effect, so they can help to achieve this remis- sion goal in a safer way (Fig. 5). Intensive glycemic control in T2DM increases the likelihood of remission at the earlier stage of the disease and helps to reduce the complications associated with T2DM even if remission is not achieved [144,145]. How- ever, we should be wary of the side effects that accompany these methods, which cause dramatic changes in the body. From the perspective of long-term survival, it is necessary to pay atten- tion to the risk of hypoglycemia in elderly patients, and addi- tional research is needed on the long-term medical outcomes of diabetic remission [146,147]. Patients who have previously been diagnosed with diabetes are exposed to the risks of diabe- tes-related complications, even in patients who have improved and confirmed remission. Support and continuous medical su- pervision from family members, friends and medical staff are essential so that they can maintain a healthy lifestyle and screen for comorbidities associated with diabetes. T2DM is not a fate for individuals to helplessly accept. We have discussed the re- mission of T2DM, which can be achieved through a personal- ized approach. It may be necessary to change the concept of T2DM towards that of an urgent condition that requires rapid intervention rather than a chronic, progressive disease. We must grasp this paradigm shift in our understanding of T2DM for the benefit of our patients as endocrine experts.

# CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was re- ported.

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