Journal of Obesity & Metabolic Syndrome 2022;31:123-133
https://doi.org/10.7570/jomes22001

Review

jomes
pISSN 2508-6235
eISSN 2508-7576

Type 2 Diabetes Remission with Significant Weight Loss: Definition and Evidence-Based Interventions

Jung Hae Ko, Tae Nyun Kim*

Division of Endocrinology and Metabolism, Department of Internal Medicine, Inje University College of Medicine, Busan, Korea

Type 2 diabetes (T2D) has long been regarded as an incurable and chronic disease according to conventional management methods. Clinical and pathophysiological studies on the natural course of T2D have shown that blood glucose control worsens with an increase in the number of required anti-hyperglycemic agents, as β-cell function progressively declines over time. However, recent studies have shown remission of T2D after metabolic surgery, intensive lifestyle modification, or medications, raising the possibility that β-cell function may be preserved or the decline in β-cell function may even be reversible. The World Health Organization as well as the American Diabetes Association and the European Association for the Study of Diabetes recognize remission as an appropriate management aim. In the light of the state of evidence for T2D reversal, physicians need to be educated on treatment options to achieve T2D remission so that they can actively play a part in counseling patients who may wish to explore these approaches to their disease. This review will introduce each of these approaches, summarizing their beneficial effects, supporting evidence, degree of sustainability, and challenges to be addressed in the future.

Key words: Type 2 diabetes mellitus, Remission, Weight loss

Received January 20, 2022
Reviewed February 14, 2022
Accepted March 15, 2022

*Corresponding author
Tae Nyun Kim

https://orcid.org/0000-0001-6568-2469

Division of Endocrinology and Metabolism, Department of Internal Medicine, Inje University Haeundae Paik Hospital, 875 Haeun-daero, Haeundae-gu, Busan 48108, Korea
Tel: +82-51-797-2063
Fax: +82-51-797-2070
E-mail: kimtn031@gmail.com

INTRODUCTION

Type 2 diabetes (T2D) is a chronic and progressive disease in which the risks of microvascular and macrovascular complications are all strongly associated with chronic hyperglycemia.[1] Prospective observational studies have demonstrated blood glucose control worsens with an increase in the number of required anti-hyperglycemic agents in T2D.[2] In view of this clinical fact, it is a usual practice to inform patients at the time of T2D diagnosis that they have a lifelong disease that must be accepted and managed as early as possible. Nevertheless, patients with T2D tend to not comply with chronic treatment, especially lifelong medications, at the time of diagnosis and thereafter. One of the questions that physicians are still asked the most is "can I stop the medication after a while?" Recent studies and trials have brought about a change in the treatment of T2D. The American Diabetes Association (ADA) now recognizes remission as an appropriate target of treatment.[3] Although T2D remains thought of as a chronic and irreversible disease, opinion is changing.

The 2016 World Health Organization global report on diabetes acknowledged that T2D reversal can be achieved through a very low-calorie diet or metabolic surgery.[4] Before looking at how to revert T2D, it may be important to identify the exact definition of it. Unlike curable diseases, diabetes is defined as a chronic state of hyperglycemia, which exists on a continuous value. Medically, cure refers to restoration from an irreversible condition to good health, while remission is defined as a transient disease-naïve status. Many doctors consider the real cure to be limited to acute illnesses. In 2009, the ADA expressed opinions regarding the type of consensus statement.[5] For a chronic disease such as T2D or hypertension, it

Table 1. Definition and glycemic criteria for diagnosing type 2 diabetes remission

	2009 ADA statements[5]	2021 ADA consensus report[6]
Definition	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 ≥ 5 year's duration	Remission • Hyperglycemia below diagnostic thresholds for diabetes • At least 3 months after cessation of pharmacotherapy or surgery
Glycemic criteria	Partial remission HbA1c < 6.5% and/or FPG 100–125 mg/dL Complete remission HbA1c < 5.7% and FPG < 100 mg/dL	Remission HbA1c < 6.5% (GMI or eHbA1c < 6.5% in some circumstances)

ADA, American Diabetes Association; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; GMI, glucose management indicator; eHbA1c, estimated HbA1c by continuous glucose monitoring.

may be more appropriate to use the term remission rather than cure. The authors used glycosylated hemoglobin (HbA1c) and fasting plasma glucose levels to dictate remission, and they defined remission as a condition achieving normoglycemia without active pharmacological therapy. Remission was classified as partial or complete, partial remission was defined as sub-diabetic hyperglycemia below diagnostic thresholds for diabetes (HbA1c < 6.5%), and complete remission was a return to normal glycemic metabolic state (HbA1c < 5.7%). In both groups, the duration was > 1 year. In addition, prolonged remission is a complete remission that lasts for ≥ 5 years in the absence of pharmacotherapy (Table 1).

Despite the debates, a new consensus report by the ADA was published in August 2021.[6] The authors agreed that the term "cure" should be avoided in the context of clinical management of T2D. To determine the glycemic criteria for diagnosing T2D remission, they still favored HbA1c levels below the level currently used for the initial diagnosis of T2D (6.5%). However, many factors, such as hemoglobinopathy, can affect the HbA1c level. Thus, the estimated HbA1c (eHbA1c) or glucose management indicator (GMI) determined by measuring the 24-hour mean glucose concentration using continuous glucose monitoring was recommended. Unlike before, maintenance of eHbA1c or GMI < 6.5% without oral medication for > 3 months was considered remission in all circumstances (Table 1).

The factors predicting remission of T2D are weight loss, baseline pancreatic function, and diabetes duration.[7,8] Although the factors may vary depending on the treatment strategy, significant weight loss is the most common predictive factor in all treatment options. Obesity is a primary factor of insulin resistance, and it also affects β-cell decompensation.[9] According to the twin cycle hypothesis, calorie excess over a long period of time causes fat accumulation and insulin resistance in the liver.[10] The consequent hyperinsulinemia further increases the conversion of excess calories into hepatic fat. In addition, excess hepatic fat causes increased fat delivery to many tissues, including the pancreatic islet. Fat accumulation within the pancreas can cause a progressive decrease in insulin production. Conversely, weight loss can reverse the entire process. For this reason, weight loss of 5%–10% can prevent overt diabetes.[11] There are many ways to lose weight, but the main idea behind all is the achievement of a negative energy balance. Of course, many ways to lose weight require a lot of cost and effort, but when analyzing lifetime cost per quality-adjusted life-year, even if all costs are considered, intensive intervention was predicted to be more effective and cost-saving in patients with T2D compared to usual care.[12]

A significant number of studies have shown that diabetes remission can be achieved using metabolic surgery or intensive lifestyle modification. Other approaches, such as new medications, have also shown the possibility of diabetes remission with an excellent effect.[13-15] This article will review each of these approaches, summarizing their effectiveness, supporting evidence, degree of sustainability, and challenges to be solved in the future.

REMISSION AFTER METABOLIC SURGERY

Metabolic surgery has produced immediate and dramatic improvements in glucose levels in obese patients with diabetes for many years. The ADA guidelines for obesity management for T2D patients state that metabolic surgery should be recommended to treat T2D in obese patients such as those with a body mass index (BMI) of ≥ 40 kg/m^2 (BMI of ≥ 37.5 kg/m^2 in Asians).[16] It also may be considered to treat T2D patients with BMIs of 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asians) who do not maintain weight loss with non-surgical strategies.[16] Clinical studies show the significant effects of surgery to induce remission.[17] It was observed that the remission of diabetes occurred when surgical procedures like gastric band, Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and biliopancreatic diversion were performed.[18] Several large cohort studies comparing metabolic surgery to conventional treatment have confirmed the superiority of metabolic surgery in the aspect of achieving diabetes remission.[19-23] In the Swedish Obesity Subjects (SOS) study, weight decreased by 23.4% in the metabolic group. Also, the rate of diabetes remission was up to 72.4% compared to 16.4% in the medically treated control group at 2 years.[19] In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, obese patients with uncontrolled T2D were randomized to intensive medical therapy, SG, or RYGB.[24] The primary endpoint was the proportion of patients with HbA1c ≤ 6.0% at 12 months after treatment. The proportion of patients with the primary endpoint was 12% in the pharmacologic therapy group versus 42% in the gastric-bypass group and 37% in the SG group. Five-year outcome data also showed the same result, but with approximately half of patients ultimately relapsing.[25]

What makes diabetes improve after surgery? Glycemic improvement after metabolic surgery is partly associated with weight loss. The glucose monitoring pattern of metabolic surgery is the rapid improvement in glycemic control in advance of weight loss. The mechanism of weight-independent improvements in glucose homeostasis is due to alterations in gut hormones. Glucagon-like peptide 1 (GLP-1) is a gut hormone secreted by intestinal neuroendocrine L-cells. Following metabolic surgery, postprandial GLP-1 levels are increased, leading to improved glucose sensitivity and postprandial glucose levels.[26-28] Also, there is a difference in the blood glucose-lowering effect depending on the surgical method. According to a meta-analysis study that reviewed 16 randomized controlled trials, RYGB led to a lower fasting blood glucose and HbA1c than SG.[29] Similarly, in the case of diabetes remission, there was variability in the remission rate by surgical procedure.[30] Despite this variability, metabolic surgery has a higher remission rate than medical therapy. In another meta-analysis of clinical trials, the remission rate of T2D was ≥ 5 times higher in surgically managed patients and possibly as much as 22 times higher.[31]

While metabolic surgery has a significant ability to induce remission of T2D, remission is not attained in all patients. In a 15-year follow-up study of SOS, the remission rate decreased from 72.3% at 2 years to 38.1% at 10 years and 30.4% at 15 years after surgery but remained higher than that in the controls.[32] When analyzing the association of metabolic surgery with microvascular and macrovascular complications of T2D, the incidence of microvascular complications (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.34–0.56; $P < 0.001$) and macrovascular complications (HR, 0.68; 95% CI, 0.54–0.85; $P < 0.001$) has decreased in the metabolic surgery group.[32] A short duration of T2D at baseline was associated with maintenance of remission and low complication rates. In conclusion, if severely obese patients are diagnosed with T2D and are expected to have a difficulty in managing with medical therapy, rapid decision-making regarding surgical procedures may help patients to achieve remission and have low complication rates.

REMISSION BY INTENSIVE LIFESTYLE MODIFICATION

People with newly diagnosed with diabetes are recommended to receive diabetes self-management education and support (DSMES).[33] The most important part of DSMES is determining what to eat. The goals of the DSMES are as follows: (1) achieving and maintaining body weight goals; (2) attaining individualized glycemic, blood pressure, and lipid goals; and (3) delaying or preventing complications of diabetes. Therefore, every obese patient with diabetes is recommended to lose weight by > 5% to achieve beneficial outcomes.[34] In particular, obese patients with pre-diabetes should increase their target weight loss goal by up to 7%–10% to prevent or

delay getting T2D.[35] However, more intensive weight loss (15%) may be appropriate to maximize benefit among patients with T2D.[36,37] In the Action for Health in Diabetes (Look AHEAD) trial,[38] an intensive lifestyle intervention (ILI) induced diabetes remission in the intervention group more than in the control group. In the Look AHEAD trial, obese patients with T2D were randomly assigned to ILI or diabetes support and education (DSE). The ILI group was significantly more likely to achieve diabetes remission, with prevalence rates of 11.5% during the first year and 7.3% at year 4 compared to that of 2.0% for the DSE group at each point.[38] The results of the Look AHEAD study were intensified and re-evaluated in the Diabetes Remission Clinical Trial (DiRECT).[36] In the Look AHEAD trial, diabetes remission was not the primary endpoint, but DiRECT was a trial targeting diabetes remission using a structured liquid diet formula to reduce weight in primary care practices in the United Kingdom.[36] In that study, total diet replacement (825–852 kcal/day formula diet for 3–5 months), withdrawal of anti-diabetic and anti-hypertensive drugs, and intensified lifestyle management support for long-term weight loss maintenance were conducted. Diabetes remission at 1 year (HbA1c ≤6.5% after 2 months off all anti-diabetic medications) was achieved in 46% of the intervention group and 4% of the control group.[36] In particular, 36 patients losing ≥15 kg maintained diabetes remission up to 86%. However, in a follow-up study, weight regain was demonstrated.[39] At 2 years, only 11% of participants had a weight loss of ≥15 kg, and 36% of them in the intervention group had diabetes remission. Nevertheless, sustained remission at 2 years was observed in more than one third of patients with T2D. Therefore, maintaining remission is associated with the extent of lasting weight loss.[39] To maintain weight loss, the role of registered dietitian nutritionists (RD/RDN) who have professional knowledge and skills in providing diabetes-specific medical nutritional therapy (MNT) is inevitable. MNT provided by an RD/RDN is associated with HbA1c reductions of 0.3%–2.0% among patients with T2D.[40] In Korea, diabetes educators have a special license for MNT education. A specialist is needed because there is no uniform eating pattern among patients with T2D. Instead, there is a belief that meal planning should be individualized, such as in medical care. Various eating plans have been developed to control weight and reduce cardiovascular risk levels in people with T2D. This includes structured low-calorie meal plans with meal replacements,[36,41,42] a Mediterranean-style eating pattern,[43] and low-carbohydrate meal plans with additional support.[44] However, no single approach has been proven to be superior over others.

The lifestyle program for obese patients with T2D aims to reduce the energy intake to 500–750 kcal/day less than what is recommended, which is approximately 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, depending on the individual's baseline body weight.[16] To avoid weight regain, ILIs, such as long-term (≥1 year) comprehensive weight-loss maintenance programs with trained interventionists, should be introduced. Weight regain appears to be more common in patients on very-low-calorie diets and meal-replacement plans; therefore, interventions should include long-term, comprehensive strategies to maintain weight loss.[45] Furthermore, diet selection should take into account the patient's health status and preferences, including a determination of food availability and other cultural situations that may affect dietary patterns.[46] In short, dietary recommendations should be individualized according to the patient's systemic, structural, and socioeconomic factors. Therefore, in order to ensure remission, maintaining weight loss is required, and continuous attention and the efforts of several specialists must be combined. This is essential for the interest and efforts of medical professionals in MNT education.

REMISSION AFTER INCRETIN HORMONE THERAPY

In a previous study, glucose levels were normalized by early combination therapy (vildagliptin and metformin) in patients with a short duration of diabetes.[47] Therefore, it is suggested that lowering the target HbA1c level is necessary, and the importance of diabetes remission is emphasized. As mentioned before, metabolic surgery is a good therapeutic option, but it has the limitation of that patients receiving treatment must exist within a restrictive body weight or BMI range (BMI ≥40 kg/m^2; BMI ≥37.5 kg/m^2 in Asians). In addition, intensive lifestyle modifications can make it difficult for patients to keep weight off and remain in diabetes remission. Thus, achieving normoglycemia on therapy using lifestyle modifications and drug therapy promoted sustained diabetes remission safely.[48] After achieving normoglycemia, if conducting drug tapering while

maintaining the body weight, remission should be sustained. However, there are two essential factors in drug-treatment strategies for diabetes remission. One is a low risk of hypoglycemia; if hypoglycemia occurs frequently, a drug with high efficacy cannot be used in sufficient dosages to achieve normoglycemia. Second, the pharmacologic therapies need to be beneficial for weight loss. In general, both sodium glucose co-transporter 2 inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP-1 RAs) cause weight loss.[49] However, the efficacy of weight loss with SGLT2is is less than that with GLP-1 RAs. A drug type that meets both of these points is GLP-1 RAs. In particular, liraglutide and semaglutide were initially developed for the treatment of T2D but were found to be effective in reducing glucose levels and weight.[50-52] GLP-1 RAs are attractive agents for the management of obesity owing to the actions of GLP-1 on appetite and energy balance and are highly effective in lowering glucose levels. GLP-1 is released from L-cells and able to stimulate insulin secretion in patients with T2D.[53] Another important role of GLP-1 is delaying gastric emptying; on the other hand, in the central nervous system, GLP-1 receptors are located in the hypothalamus, which is the part that regulates food intake.[54] Therefore, GLP-1 RAs induce weight loss through multiple mechanisms. Meanwhile, in the 2021 ADA guideline, it was announced that GLP-1 RAs are preferred over insulin because of their high efficacy and safety.[55] Once-daily subcutaneous administration of liraglutide and once-weekly semaglutide therapy were approved as anti-diabetic medications.[56,57] Consequently, higher doses of both were developed for the treatment of obesity as well as glucose control in people with or without T2D.[13,58] Liraglutide 3.0 mg is currently approved and used in Korea for the treatment of obesity. In the Satiety and Clinical Adiposity—Liraglutide Evidence in Non-diabetic and Diabetic Individuals (SCALE) obesity and pre-diabetes trials, liraglutide 3.0 mg reduced body weight compared to the placebo (achieving a difference of –5.6 kg; 95% CI, –6.0 to –5.1 kg; $P < 0.001$).[14] Also, at 3 years of follow-up, the time to onset of T2D was 2.7 times longer with liraglutide than with placebo (95% CI, 1.9–3.9; $P < 0.0001$), corresponding to a HR of 0.21 (95% CI, 0.13–0.34).[59] The U.S. Food and Drug Administration approved semaglutide 2.4 mg (Wegovy; Novo Nordisk, Bagsværd, Denmark) for weight loss in adults who are obese or overweight with ≥ 1 weight-related condition (e.g., high blood pressure, T2D, or high cholesterol) in June 2021. This drug has not yet been approved in Korea, but its efficacy is promising. In the Semaglutide Treatment Effect in People with Obesity (STEP) 2 trial, the estimated change in mean body weight from baseline to week 68 was –9.6% (standard error, 0.4). The HbA1c concentration improved from baseline to week 68 in those who received semaglutide 2.4 mg by –1.6% (standard error, 0.1).[13] Patients who achieved a ≥ 10% reduction in their baseline body weight at week 68 with semaglutide 2.4 mg totaled 45.6%, and the proportion of patients who took semaglutide 2.4 mg and achieved HbA1c levels of ≤ 6.5% was 67.5%.[13] The results showed that both the glucose-lowering effect and weight loss were as meaningful as seen with metabolic surgery. Most recently, a glucose-dependent insulinotropic polypeptide (GIP)–GLP-1 dual agonist, tirzepatide, showed impressive results in obese diabetic patients.[15] GIP, a 42-amino acid polypeptide, secreted from endocrine K-cells of the upper small intestinal epithelium, was the first incretin.[60] GIP enhances insulin secretion in a glucose-dependent manner and promotes weight loss by signaling satiety through its receptors in the hypothalamus.[61] Co-administration of GIP and a GLP-1 RA has an additive effect in increasing insulin response compared to separate administration of each hormone in healthy individuals.[62] However, in people with T2D, co-administration of GIP and GLP-1 over a short time did not generate an insulin response greater than that of GLP-1 administration alone.[63] Tirzepatide is a dual GIP–GLP-1 RA formulated as a synthetic linear peptide containing 39 amino acids based on the native GIP sequence. It has a comparable GIP receptor–binding affinity to native GIP and five times lower GLP-1 receptor affinity than that of native GLP-1.[64] The SURPASS trials were designed to assess the efficacy and safety of tirzepatide as a treatment to improve glycemic control in people with T2D. In SURPASS-1, tirzepatide led to robust improvements in glycemic control and body weight. Tirzepatide 15 mg caused a 2.07% HbA1c reduction and a 9.5-kg weight loss. The proportion of patients who achieved HbA1c levels of ≤ 6.5% was 86% in the tirzepatide 15 mg group.[15] Patients who achieved a ≥ 10% reduction in the tirzepatide 15 mg group totaled 47%. Furthermore, in the SURPASS-2 trial comparing tirzepatide to semaglutide 1 mg, tirzepatide was non-inferior and superior to semaglutide.[65] On the other hand, no clinically significant hypoglycemia (< 54 mg/dL) was reported in either trials (Figs. 1 and 2). These characteristics

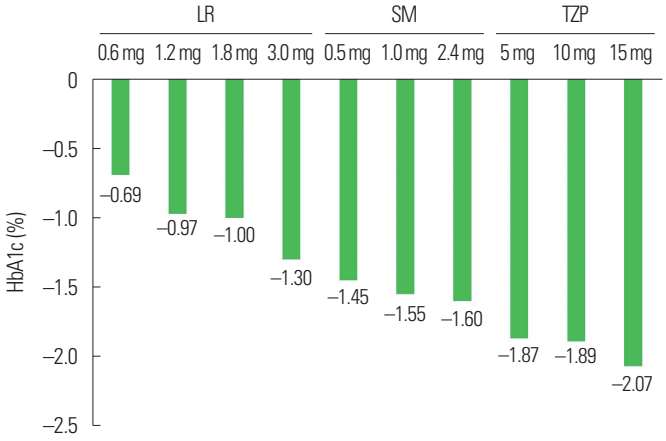

Figure 1. Efficacy of incretin hormones—glycosylated hemoglobin (HbA1c) change from baseline. LR, liraglutide; SM, semaglutide; TZP, tirzepatide. LR 0.6 mg, 1.2 mg, and 1.8 mg (LEAD2 study[66]); LR 3.0 mg (SCALE study[13]); SM 0.5 mg and 1.0 mg (SUSTAIN 1 study[67]); SM 2.4 mg (STEP2 study[12]); TZP 5 mg, 10 mg, and 15 mg (SURPASS 1 study[14]).

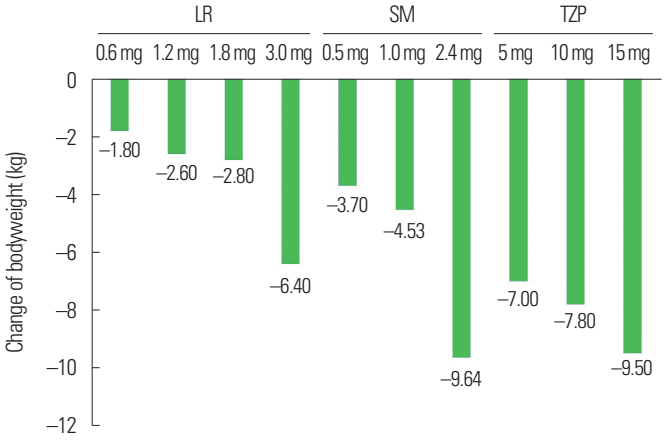

Figure 2. Efficacy of incretin hormones—body weight change from baseline. LR, liraglutide; SM, semaglutide; TZP, tirzepatide. LR 0.6 mg, 1.2 mg, and 1.8 mg (LEAD2 study[66]); LR 3.0 mg (SCALE study[13]); SM 0.5 mg and 1.0 mg (SUSTAIN 1 study[67]); SM 2.4 mg (STEP2 study[12]); TZP 5 mg, 10 mg, and 15 mg (SURPASS 1 study[14]).

could satisfy all the requirements for diabetes remission. In addition to tirzepatide, which is not yet being used clinically, incretin hormones are used to maintain weight loss and diabetes remission by combining metabolic surgery and intensive lifestyle modifications.[68,69] In the case of a relatively short duration of T2D, the weight loss caused by GLP-1 RAs alone may be sufficient to achieve diabetes remission, and combination therapy could maintain remission. By definition, remission cannot be diagnosed in the setting of ongoing pharmacotherapy.[6] However, significant weight loss and glucose normalization even after stopping incretin hormones can help to maintain diabetes remission.

CONCLUSION

Obesity and T2D are interrelated conditions that share several pathophysiological mechanisms that are frequently observed to lead to cardiovascular complications. Weight loss in overweight and obese patients with T2D, whether achieved by lifestyle intervention, pharmacotherapy, or metabolic surgery, contributes to improved cardiovascular complications. In the 15-year follow-up analysis of the SOS, rates of microvascular and macrovascular complications were lower in the surgical group than the control group.[32] In the DiRECT study, patients' the mean blood pressure was decreased significantly from the start of total diet replacement and they stopped anti-hypertensives, but 72% (50/69) required re-introduction of anti-hypertensive medications by the end of the trial.[70] Therefore, a study with long-term follow-up is required to assess the risk of complications of diabetes in the context of other strategies of weight loss in diabetic patients.

The next most important factor is weight gain. Unfortunately, a definition of weight regain has not been established, and the association between regain and remission failure has not been clearly established. In general, if the return to the original weight is defined as weight regain, significant weight regain is rare for patients undergoing RYGB. Nearly one in three patients undergoing SG regained all their lost weight by 4 years after surgery.[71] In the DiRECT study, to maintain the lost weight, the authors changed participants' meal patterns variously.[72] In the case of pharmacotherapy, some patients with early diabetes were able to achieve remission after short-term intensive medical therapy,[73] but limited in incretin therapies. There is no study yet on whether remission is maintained after withdrawal of the drug; therefore, lifetime therapy may be required to maintain weight loss. In particular, it has been reported that the HbA1c-lowering efficacy of GLP-1 RAs is greater in Asian-dominant groups than in non–Asian-dominant groups.[66] Therefore, higher achievement rates in diabetes remission brought on by incretin hormone therapy is expected in Korea. To assess the durability of diabetes remission and ethnic differences in incretin therapy, further studies will be required.

In conclusion, diabetes remission due to weight loss requires the

cooperation of various specialists under an individualized approach paradigm because there are several ways to attain it and it is difficult to maintain.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2018S1A5A8027802).

AUTHOR CONTRIBUTIONS

Study concept and design: all authors; analysis and interpretation of data: all authors; drafting of the manuscript: all authors; critical revision of the manuscript: all authors; administrative, technical, or material support: all authors; and study supervision: all authors.

REFERENCES

1. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.
2. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005-12.
3. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669-701.
4. World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016.
5. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, et al. How do we define cure of diabetes? Diabetes Care 2009;32:2133-5.
6. Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus report: definition and interpretation of remission in type 2 diabetes. Diabetologia 2021;64:2359-66.
7. Thom G, Messow CM, Leslie WS, Barnes AC, Brosnahan N, McCombie L, et al. Predictors of type 2 diabetes remission in the Diabetes Remission Clinical Trial (DiRECT). Diabet Med 2021;38:e14395.
8. Park JY. Prediction of type 2 diabetes remission after bariatric or metabolic surgery. J Obes Metab Syndr 2018;27:213-22.
9. Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab 2011;96:1654-63.
10. Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. Diabetologia 2008;51:1781-9.
11. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
12. Xin Y, Davies A, Briggs A, McCombie L, Messow CM, Grieve E, et al. Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the Diabetes Remission Clinical Trial (DiRECT)/Counterweight-Plus weight management programme. Diabetologia 2020;63:2112-22.
13. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971-84.
14. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11-22.
15. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase

3 trial. Lancet 2021;398:143-55.
16. American Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S100-10.
17. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it?: an operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995;222:339-52.
18. Yu J, Zhou X, Li L, Li S, Tan J, Li Y, et al. The long-term effects of bariatric surgery for type 2 diabetes: systematic review and meta-analysis of randomized and non-randomized evidence. Obes Surg 2015;25:143-58.
19. Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93.
20. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg 2003;238:467-85.
21. Pournaras DJ, Osborne A, Hawkins SC, Vincent RP, Mahon D, Ewings P, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes. Ann Surg 2010;252:966-71.
22. Jakobsen GS, Småstuen MC, Sandbu R, Nordstrand N, Hofsø D, Lindberg M, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. JAMA 2018;319:291-301.
23. Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. Effect of Roux-en-Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population-based matched cohort study. Diabetologia 2019;62:611-20.
24. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012;366:1567-76.
25. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes: 5-year outcomes. N Engl J Med 2017;376:641-51.
26. Falkén Y, Hellström PM, Holst JJ, Näslund E. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day three, two months, and one year after surgery: role of gut peptides. J Clin Endocrinol Metab 2011;96:2227-35.
27. Dirksen C, Bojsen-Møller KN, Jørgensen NB, Jacobsen SH, Kristiansen VB, Naver LS, et al. Exaggerated release and preserved insulinotropic action of glucagon-like peptide-1 underlie insulin hypersecretion in glucose-tolerant individuals after Roux-en-Y gastric bypass. Diabetologia 2013;56:2679-87.
28. Bose M, Teixeira J, Olivan B, Bawa B, Arias S, Machineni S, et al. Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. J Diabetes 2010;2:47-55.
29. Hayoz C, Hermann T, Raptis DA, Brönnimann A, Peterli R, Zuber M. Comparison of metabolic outcomes in patients undergoing laparoscopic Roux-en-Y gastric bypass versus sleeve gastrectomy: a systematic review and meta-analysis of randomised controlled trials. Swiss Med Wkly 2018;148:w14633.
30. Affinati AH, Esfandiari NH, Oral EA, Kraftson AT. Bariatric surgery in the treatment of type 2 diabetes. Curr Diab Rep 2019;19:156.
31. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ 2013;347:f5934.
32. Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden Å, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297-304.
33. American Diabetes Association. 5. Facilitating behavior change and well-being to improve health outcomes: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S53-72.
34. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet

2015;115:1447-63.
35. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102-7.
36. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541-51.
37. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481-6.
38. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489-96.
39. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019;7:344-55.
40. Franz MJ, MacLeod J, Evert A, Brown C, Gradwell E, Handu D, et al. Academy of Nutrition and Dietetics Nutrition Practice Guideline for type 1 and type 2 diabetes in adults: systematic review of evidence for medical nutrition therapy effectiveness and recommendations for integration into the nutrition care process. J Acad Nutr Diet 2017;117:1659-79.
41. Hamdy O, Mottalib A, Morsi A, El-Sayed N, Goebel-Fabbri A, Arathuzik G, et al. Long-term effect of intensive lifestyle intervention on cardiovascular risk factors in patients with diabetes in real-world clinical practice: a 5-year longitudinal study. BMJ Open Diabetes Res Care 2017;5:e000259.
42. Mottalib A, Salsberg V, Mohd-Yusof BN, Mohamed W, Carolan P, Pober DM, et al. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. Nutr J 2018;17:42.
43. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34.
44. Saslow LR, Daubenmier JJ, Moskowitz JT, Kim S, Murphy EJ, Phinney SD, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes 2017;7:304.
45. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring) 2006;14:1283-93.
46. Leung CW, Epel ES, Ritchie LD, Crawford PB, Laraia BA. Food insecurity is inversely associated with diet quality of lower-income adults. J Acad Nutr Diet 2014;114:1943-53.
47. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394:1519-29.
48. McInnes N, Smith A, Otto R, Vandermey J, Punthakee Z, Sherifali D, et al. Piloting a remission strategy in type 2 diabetes: results of a randomized controlled trial. J Clin Endocrinol Metab 2017;102:1596-605.
49. Brown E, Wilding JP, Barber TM, Alam U, Cuthbertson DJ. Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: mechanistic possibilities. Obes Rev 2019;20:816-28.
50. Bode BW. Design, findings and implications of the liraglutide phase III clinical trial program. Clin Invest 2012;2:59-72.
51. Aroda VR, Ahmann A, Cariou B, Chow F, Davies MJ, Jódar E, et al. Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: insights from the SUSTAIN 1-7 trials. Diabetes Metab 2019;45:409-18.
52. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: The PIONEER programme. Diabetes Obes Metab 2020;22:1263-77.
53. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. Diabetes Obes Metab 2018;20 Suppl 1:5-21.
54. Farr OM, Sofopoulos M, Tsoukas MA, Dincer F, Thakkar B, Sahin-Efe A, et al. GLP-1 receptors exist in the parietal cortex,

hypothalamus and medulla of human brains and the GLP-1 analogue liraglutide alters brain activity related to highly desirable food cues in individuals with diabetes: a crossover, randomised, placebo-controlled trial. Diabetologia 2016;59:954-65.
55. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care 2021;44(Suppl 1):S111-24.
56. Vilsbøll T, Zdravkovic M, Le-Thi T, Krarup T, Schmitz O, Courrèges JP, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. Diabetes Care 2007;30:1608-10.
57. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol 2018;6:275-86.
58. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687-99.
59. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DC, Van Gaal L, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399-409.
60. Dupre J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab 1973;37:826-8.
61. Adriaenssens AE, Biggs EK, Darwish T, Tadross J, Sukthankar T, Girish M, et al. Glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. Cell Metab 2019;30:987-96.
62. Nauck MA, Bartels E, Orskov C, Ebert R, Creutzfeldt W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. J Clin Endocrinol Metab 1993;76:912-7.
63. Mentis N, Vardarli I, Köthe LD, Holst JJ, Deacon CF, Theodorakis M, et al. GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes. Diabetes 2011;60:1270-6.
64. Coskun T, Sloop KW, Loghin C, Alsina-Fernandez J, Urva S, Bokvist KB, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. Mol Metab 2018;18:3-14.
65. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med 2021;385:503-15.
66. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:900-9.
67. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol 2017;5:251-60.
68. Miras AD, Pérez-Pevida B, Aldhwayan M, Kamocka A, McGlone ER, Al-Najim W, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2019;7:549-59.
69. Lundgren JR, Janus C, Jensen SB, Juhl CR, Olsen LM, Christensen RM, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. N Engl J Med 2021;384:1719-30.
70. Leslie WS, Ali E, Harris L, Messow CM, Brosnahan NT, Thom G, et al. Antihypertensive medication needs and blood pressure control with weight loss in the Diabetes Remission Clinical Trial (DiRECT). Diabetologia 2021;64:1927-38.
71. Maciejewski ML, Arterburn DE, Van Scoyoc L, Smith VA, Yancy WS Jr, Weidenbacher HJ, et al. Bariatric surgery and

long-term durability of weight loss. JAMA Surg 2016;151:1046-55.
72. Brosnahan N, Leslie W, McCombie L, Barnes A, Thom G, McConnachie A, et al. Brief formula low-energy-diet for relapse management during weight loss maintenance in the Diabetes Remission Clinical Trial (DiRECT). J Hum Nutr Diet 2021;34:472-9.
73. McInnes N, Hall S, Sultan F, Aronson R, Hramiak I, Harris S, et al. Remission of type 2 diabetes following a short-term intervention with insulin glargine, metformin, and dapagliflozin. J Clin Endocrinol Metab 2020;105:dgaa248.