

Review Article



Strategies to Maintain the Remission of Diabetes Following Metabolic Surgery

Mi Kyung Kim ,^{1,2} Hye Soon Kim ^{1,2}

¹Department of Internal Medicine, Keimyung University School of Medicine, Dongsan Hospital, Daegu, Korea

²Center of Bariatric and Metabolic Surgery, Keimyung University, Dongsan Hospital, Daegu, Korea



Received: Sep 26, 2023

Revised: Nov 19, 2023

Accepted: Nov 20, 2023

Published online: Nov 29, 2023

Corresponding author:

Hye Soon Kim

Department of Internal Medicine, Keimyung University, Dongsan Hospital, 1095 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea.

Tel: +82-258-4921

Fax: +82-53-258-4990

Email: hsk12@dsmc.or.kr

This article was presented at the 32nd Spring Congress of the Korean Society for Metabolic and Bariatric Surgery.

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ORCID iDs

Mi Kyung Kim

<https://orcid.org/0000-0001-5750-3598>

Hye Soon Kim

<https://orcid.org/0000-0001-6298-3506>

Funding

This study was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) grant, funded by the Ministry of Science, ICT and Future Planning (NRF-2021R111A3059150), and

ABSTRACT

Obesity is a major risk factor for type 2 diabetes mellitus (T2DM). Bariatric surgery is the most effective means of inducing weight loss, and can ameliorate or induce the remission of obesity-related metabolic comorbidities, including T2DM. The guidelines for the management of T2DM emphasize weight management and recommend metabolic surgery for the treatment of T2DM accompanied by obesity. However, despite the clear beneficial effects of metabolic surgery, only 20–50% of patients who experience remission will stay in remission over the long term. Moreover, the beneficial effects of metabolic surgery tend to diminish with time, and a subset of patients experience a relapse of their diabetes. Therefore, in the present review, we discuss potential strategies for the maintenance of diabetic remission following metabolic surgery.

Keywords: Obesity; Type 2 diabetes mellitus; Bariatric surgery

INTRODUCTION

Obesity is a major risk factor for type 2 diabetes mellitus (T2DM). According to the Korean Obesity Fact Sheet, someone in their 40s with obesity is at a 5.1-times higher risk of diabetes, and someone in their 60s is at a 1.8-times higher risk, than individuals who do not have obesity [1]. In addition, approximately half of patients with diabetes in Korea have obesity and 63.3% of patients with diabetes have abdominal obesity [2]. Therefore, obesity management is a very important component of diabetes management. Recently, a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended a holistic patient-centered approach to the management of T2DM, with an emphasis on weight management [3]. Likewise, the clinical practice guidelines for diabetes in Korea also recommend weight reduction and maintenance [4]. It recommends that adults with obesity and T2DM should lose at least 5% of their body weight through lifestyle modifications and subsequently maintain their weight. If patients with a body mass index (BMI) ≥ 25 kg/m² fail to lose weight through diet, physical activity, and behavior counseling, the use of anti-obesity medications can be considered. If the use of an anti-obesity drug does not result in a loss of >5% of body weight within 3 months, then the drug should be changed or discontinued [4].

Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare (HI22C0729), Republic of Korea.

Conflict of Interest

None of the authors have any conflict of interest.

Author Contributions

Conceptualization: Kim MK, Kim HS;
Methodology: Kim MK, Kim HS; Writing - original draft: Kim MK; Writing - review & editing: Kim MK, Kim HS.

Bariatric and metabolic surgery is the most effective means of inducing weight loss [5], and its beneficial effects include the amelioration or remission of obesity-related metabolic comorbidities, including T2DM [6]. Thus, the Korean guidelines and the ADA/EASD consensus statement suggest that metabolic surgery should be considered as a treatment option for adults with T2DM who are surgical candidates [3,4,7]. The Korean guidelines recommend that bariatric surgery should be considered for patients with T2DM who have a BMI ≥ 35 kg/m², and may also be considered in those with a BMI ≥ 30 kg/m² if non-surgical treatment fails to induce weight loss or control their glycemia. Multidisciplinary care is needed before and after the bariatric surgery to ensure that it is safe and effective [4]. However, despite the substantial effects of metabolic surgery, only 20–50% of patients who experience remission stay in remission over the long term [8,9]. Moreover, the beneficial effects of metabolic surgery tend to diminish with time, and a subset of patients experience a relapse of their diabetes [10,11]. Previous studies have shown that approximately 30% of patients who initially enter remission experience relapse [12,13]. Therefore, in the present review, we discuss potential strategies for the maintenance of diabetic remission following metabolic surgery.

STRATEGIES TO INDUCE DIABETIC REMISSION

For the successful induction of diabetic remission, it is important to predict which patients are more likely to enter remission preoperatively and to manage them appropriately to prevent the postoperative relapse of T2DM.

STRATEGIES PRIOR TO SURGERY

Selection of patients

Many studies have shown that bariatric surgery is an effective means of inducing weight loss and diabetic remission [12,14], with a prevalence of postoperative remission of between 25% and 80% [14]. For successful outcomes, it is important to identify preoperative predictors of success to select patients who are most likely to benefit from bariatric surgery. Therefore, many studies have aimed to identify predictors of diabetic remission following bariatric surgery and the authors have suggested models for the prediction of remission [11-13]. Among these, the ABCD and DIaRem models are the most thoroughly validated [14].

The principal preoperative predictors that have been identified are C-peptide, the duration of diabetes, age, ethnicity, sex, the baseline glycosylated hemoglobin A1c (HbA1c), and the baseline BMI; and the most significant independent predictors of remission have been shown to be the duration of diabetes and the plasma C-peptide concentration; while the lack of insulin use and a low baseline HbA1c have been described as indirect predictors [14,15]. These parameters reflect residual β -cell function, and patients with superior β -cell function are more likely to enter remission. Therefore, patients with low plasma C-peptide concentration, who are undergoing insulin therapy preoperatively, and have had diabetes for >5–8 years may be less likely to experience remission postoperatively. Age is also considered to be a significant predictor of poorer T2DM outcomes, and the recommended age cut-off for surgery is between 40 and 50 years [15]. Conversely, patients with BMI values between 40 and 50 kg/m² are more likely to achieve remission postoperatively. However, there are few data regarding the effects of sex, ethnicity, preoperative interventions to optimize HbA1c prior to surgery, preoperative weight loss, or a preoperative diagnosis of a psychiatric disorder on the

likelihood of diabetic remission [15]. Predictors of diabetic remission among patients who have undergone surgery are similar. According to the results of a registry-based cohort study conducted in Sweden between 2007 and 2015, factors that increase the likelihood of T2DM relapse following surgery are a long duration of type 2 diabetes, high preoperative HbA1c, poor postoperative weight loss, female sex, and insulin treatment prior to surgery [11]. Advanced T2DM, an indicator of poor β -cell function, at the time of surgery [12,13] is the most significant predictor of relapse. In addition, patients who lose significantly less weight during the first year following surgery are more likely to experience relapse [13,16]. These findings imply that glycemic control should be optimized to preserve β -cell function and prevent weight regain to maintain T2DM remission following metabolic surgery.

Taking these findings together, patients with preserved β -cell function, who are not using insulin, who have been diagnosed recently, and who are young are more likely to experience diabetic remission. Therefore, the selection of the most appropriate candidates and the timing of the decision are likely to be important for the success of such surgery.

STRATEGIES FOLLOWING SURGERY

1. Glycemic control

1) Perioperative glycemic control

Many patients who undergo bariatric surgery are able to reduce the dose of or stop their oral hypoglycemic agents and insulin [17]. A retrospective review of data from the Bariatric Outcome Longitudinal Database showed that after bariatric surgery, the number of patients who use oral hypoglycemic agents is reduced by 18.8% from 28.8% to 10% and the number of patients who use insulin is reduced by 4.2% from 10% to 5.8% [18]. Thus, substantial changes in antidiabetic medication regimens are frequently possible following such surgery, and these changes may be made immediately afterwards. The study by Pories et al., [19] who suggested bariatric surgery as a treatment option for T2DM, showed that hyperglycemia is ameliorated rapidly and the required insulin dose decreases substantially during the first day following surgery, and de Oliveira et al. [20] reported that the blood glucose concentrations of patients are significantly lower by 48 hours following surgery, regardless of the use of antidiabetic medication. In addition, patients who are using insulin require an 87.5% reduction in their total daily insulin doses by postoperative day 2 [21]. Therefore, ensuring glycemic control during the rapid reductions in glucose concentrations and insulin requirements is challenging [22].

As a general rule, the guidelines [17] suggest that the use of insulin secretagogues, sodium-glucose cotransporter (SGLT) 2 inhibitors, and thiazolidinediones should be discontinued, and the insulin dose should be adjusted to minimize the risk of hypoglycemia. However, it has been suggested that the use of metformin and/or incretin-based therapies may be continued in patients with T2DM [17]. The recent practical recommendations made by the Cleveland Clinic are similar [22]: metformin administration should be stopped on the day of surgery, but if the patients experience persistent hyperglycemia, they should restart metformin at the time of discharge, if there are no concerns regarding side effects or contraindications. Because of concerns regarding the potential effects of alterations in intestinal absorption following bariatric procedures, the use of immediate-release or liquid medications is recommended, rather than the use of extended-release formulations. The discontinuation of sulfonylureas and meglinitides is recommended when the postoperative

low-calorie diet is commenced, and it is not recommended to restart their administration at the time of discharge, because of the risks of hypoglycemia and weight gain. Furthermore, thiazolidinediones should be stopped on the day of surgery and most patients do not restart them at the time of discharge. Similarly, dipeptidyl peptidase-4 (DPP-4) inhibitors should also be stopped on the day of surgery, but if the patient has persistent hyperglycemia at the time of discharge, it could be restarted, as could glucagon-like peptide 1 (GLP-1) receptor agonists (RAs), if the patient has persistent hyperglycemia and there are no relevant gastrointestinal symptoms. However, the recommendation for the day of surgery should depend on the half-life of the specific GLP-1 RA: a daily GLP-1 RA, such as exenatide, liraglutide, or oral semaglutide, should be withheld on the day of surgery; whereas there is no need to discontinue the use of a weekly GLP-1 RA, such as dulaglutide or semaglutide, prior to hospitalization, unless a dose is due to be taken on the day of surgery.

The use of SGLT 2 inhibitors should be discontinued at least 3 days before surgery, because of the associated risk of euglycemic diabetic ketoacidosis, and if a very low-calorie diet is consumed prior to surgery, physicians should consider stopping SGLT2 inhibitors. The guidelines also recommend avoiding the use of SGLT2 inhibitors during the first week following surgery, because of the risk of intravascular volume depletion and the potential for ongoing stress and poor dietary intake, which could result in diabetic ketoacidosis. It is also recommended that α -glucosidase inhibitors are discontinued by patients who plan to undergo surgery, given the possibility of a worsening of gastrointestinal symptoms [22].

The guidelines recommend that patients taking a long-acting form of insulin at bedtime consider reducing the dose by 50% the night before surgery, and that those taking such a preparation in the morning consider not administering it on the morning of the surgery. Patients administering basal-bolus insulin should also consider reducing their prandial insulin dose by at least 50% or not administering it. Prandial insulin is typically not required during hospitalization, but a sliding scale dose of rapid-acting insulin could be used every 4–6 hours, according to the hospital protocol. In addition, physicians should consider restarting long-acting insulin at a low dose if the glucose concentration is >180 mg/dL. At the time of discharge, physicians should decide whether the patient needs to continue their basal insulin based on their insulin requirements during hospitalization. Premixed insulin should be stopped on the morning of surgery and it is not recommended to restart this because of the limited caloric intake that follows bariatric surgery. If patients need insulin at the time of discharge, their premixed insulin could be exchanged for basal insulin, and administered with or without pre-prandial insulin.

2) Selection of anti-hyperglycemic drugs for the long-term treatment of poorly controlled glycemia

An endocrinology consultation should be considered for patients with poorly controlled hyperglycemia who need to modify their therapeutic regimen. In addition, patients should monitor their glucose concentrations [22]. The recent ADA/EASD consensus statement emphasized the importance of weight management and that drugs should be chosen on the basis of their efficacy with respect to weight loss. Semaglutide and tirzepatide, which are not licensed in Korea, are highly efficacious drugs; dulaglutide and liraglutide are also very effective; other GLP-1 RAs and SGLT2 inhibitors show intermediate efficacy, and DPP-4 inhibitors and metformin show less efficacy. Thus, oral hypoglycemic agents should be chosen on the basis of their efficacy with respect to weight loss, as well as their hypoglycemic and adverse effects [3].

Recently, Sudlow et al. [23] described a multi-center randomized controlled trial that aims to evaluate the safety and efficacy of target-based pharmaceutical therapy aimed at improving the long-term glycemic control of patients with T2DM following bariatric surgery. The study includes standard and intensive arms. In the standard arm, the basal insulin dose will be titrated to achieve a fasting glucose concentration of 7–9 mmol/L (126–162 mg/dL), and for any further monitoring or adjustment of the medication, the clinicians will take the primary responsibility for ensuring metabolic control. In the intensive arm, the basal insulin dose will be titrated to achieve a fasting glucose concentration of 6–8 mmol/L (106–145 mg/dL). If their fasting glucose concentrations are >7.5 mmol/L (135 mg/dL) 1 month following surgery, a GLP-1 analogue will be added, and if these remain >7.5 mmol/L (135 mg/dL), an SGLT-2 inhibitor will be added [23]. This strategy involving the stepwise addition of drugs in the intensive arm is based on the recent guidelines mentioned above [3]. The results of this study will provide valuable information regarding the improvement of long-term glycemic control following metabolic surgery.

2. Prevention of weight regain

Weight loss is an important component of the treatment of T2DM, and conversely, obesity is a major risk factor for T2DM. This implies that the prevention of weight regain following surgery is a key means of maintaining remission, and many studies have shown that weight regain is a predictor of a relapse of T2DM [13,16]. However, a clear definition of weight regain has not been established. Istfan et al. [6] defined rapid weight regain as an increase in weight of 5% within 6 months, which is considered to be clinically significant.

Multiple factors affect the level of weight regain, including behavioral, environmental, metabolic, medical, anatomic, and surgical factors. Hypoglycemia affects weight regain because it induces greater carbohydrate and sugar consumption in response to the acute symptoms [6]. Varma et al. [24] investigated whether post-bariatric hypoglycemia (PBH) affects weight regain, and found that the risk of a weight regain of >10% is significantly higher in patients who experience symptoms of PBH. Patients with PBH are susceptible to behavioral changes that aim to correct or avoid hypoglycemia, which result in weight regain [24]. Fischer et al. [25] reported that the presence of symptoms of preoperative hypoglycemia is the most significant risk factor. Once PBH has been diagnosed, medical nutrition therapy should be the first step in management. Most cases of PBH can be treated by dietary modification alone, in the form of a low-carbohydrate, low-glycemic index diet containing adequate protein and low-risk lipids, accompanied by the avoidance of rapidly-absorbed carbohydrates, alcohol, and caffeine, and adjustment of the timing of meals and snacks [17,26]. In addition, calcium channel blockers, α -glucosidase inhibitors, diazoxide, and long-acting somatostatin may be effective treatments for hypoglycemia [27]. Øhrstrøm et al. [28] studied the effects of acarbose, sitagliptin, verapamil, liraglutide, and pasireotide on PBH following Roux-en-Y gastric bypass, and found that acarbose and pasireotide reduced PBH, whereas acarbose treatment resulted in the stabilization of postprandial glycemia, and pasireotide caused hyperglycemia. Liraglutide was found not to ameliorate hypoglycemia or hyperglycemia during mixed-meal tolerance tests, but to affect food intake and stabilize postprandial glucose concentrations in some individuals, whereas sitagliptin and verapamil were found to have no effects on PBH. The effects of RYGB are thought to be mediated, at least in part, through altered GLP-1 expression and an increase in circulating insulin concentration; therefore, GLP-1 receptor antagonists are considered to be a treatment option. Craig et al. [29] reported that GLP-1 mediates the hyperinsulinemia and hypoglycemia associated with PBH, and that the GLP-1 receptor antagonist exendin (9–39) prevents this hypoglycemia. Recently, the results of a phase 2 study of avexotide were reported [30].

Avexitide [exendin (9–39)] competes with endogenous GLP-1 for the GLP-1R, and thereby counteracts the effects of excessive GLP-1 secretion, and ameliorates the symptoms of hypoglycemia and prevents hypoglycemia. Avexitide 30 mg twice daily and 60 mg once daily increased the glucose nadir by 21% and 26% and reduce the insulin peak by 23% and 21%, respectively. In addition, it significantly reduced the risk of hypoglycemia, which suggested that it may represent a promising treatment for patients with severe PBH [30].

In addition to PBH, various behavioral factors can cause weight regain. These include disordered eating habits, such as grazing and binge eating, depression, drug use, suboptimal dietary composition and choices, and a lack of compliance with the recommended follow-up visits to the clinic. Therefore, clinicians should be aware of the risk of weight regain and know how to treat this as part of a multidisciplinary team of surgeons, obesity medicine specialists, dietitians, and psychologists. It is also important that patients who undergo metabolic surgery participate in regular follow-up sessions over the long term [6].

CONCLUSIONS

Metabolic surgery is an effective treatment option for patients with T2DM. However, T2DM is a progressive disease [31,32]. The gradual increase in HbA1c in patients who undergo metabolic surgery may be the result of postoperative weight regain or the natural course of T2DM. A real-world study of bariatric surgery showed that over time, the HbA1c values of patients gradually increased following surgery [33]. This trend was similar to that identified in patients undergoing intensive medical treatment in the UK Prospective Diabetes Study [34]. Despite this natural course of T2DM, even after 6 years, the HbA1c levels of people who had undergone surgery were lower than those who had not, and half of the former did not require hypoglycemic medications and were nearly six times less likely to require insulin than the latter [33]. In addition, patients who experience a relapse of T2DM after a median of 8 years following surgery show a legacy effect on cardiovascular risk [8,13]. Thus, such a relapse in the long term should not be considered a failure, because there remain beneficial effects on cardiometabolic risk, the severity of diabetes, and the need for medication.

In this way, many patients experience remission of their diabetes, but in the long term, some who enter remission experience a relapse, which may reflect the natural course of T2DM or be the result of weight regain. Therefore, strategies are required to maintain diabetic remission (Fig. 1).

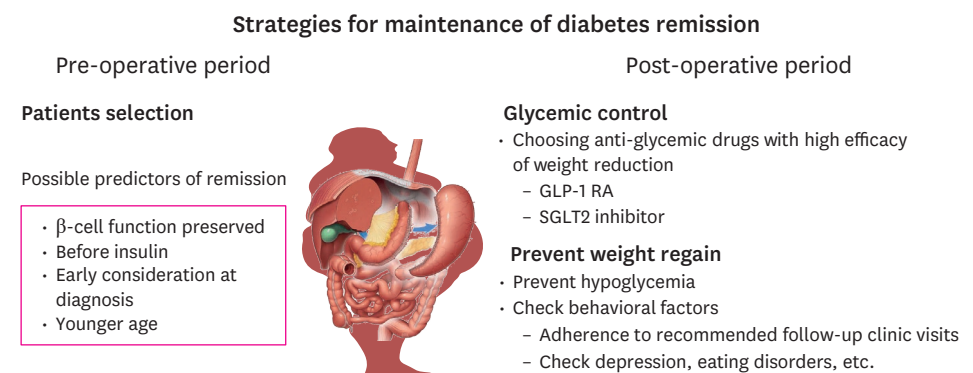


Fig. 1. Summary of strategies for maintenance of diabetes remission.

GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium glucose co-transporter 2.

Appropriate candidates for surgery are those with preserved β -cell function, with recently diagnosed diabetes, and who are young, because these characteristics are associated with a greater probability of achieving remission. In addition, postoperatively, it is important to prevent weight regain. If patients regain weight, the cause should be identified, which may be PBH, a lack of compliance with recommended follow-up visits, depression, or eating disorders, and this should be treated using a multidisciplinary approach.

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