Review Article

The metabolic effects of surgery in type 2 diabetes

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Abstract: The incidence of obesity and type 2 diabetes continues to rise by epidemic proportions. Metabolic surgery has been defined as the manipulation of a normal organ or organ system to achieve a potential health gain and used in addition to bariatric surgery. Currently, It is the only treatment modality that has the most positive and long-lasting effect on type 2 diabetes remission. Changes in the intestinal structure by surgery affect endocrine functions and digestive system physiology. A significant portion of its effects is related to weight loss. However, rapid changes, especially in gastrointestinal hormones, are responsible for the early glycemic effects. These effects occur with an increase in incretin hormone levels, a decrease in anti-incretin hormone levels, central effect through the vagus, changes in bile acid metabolism and microbiota. The reason for increase of incretin hormone levels is explained by the passage of large amounts of food into the ileum due to the anatomical alteration (hindgut hypothesis). The other alternative hypothesis is the foregut hypothesis. As a result of bypassing the upper intestinal tract, the decreased overstimulation with the interruption of the contact of foods with the duodenum and proximal jejunum probably causes the inactivation of anti-incretin factors. The clinical studies have confirmed these effects and therefore the indications for metabolic surgery have expanded. The standard recommended methods include sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB) and its modifications, biliopancreatic diversion (BPD) and its modifications. Based on meta-analysis results, gastric bypass and its modifications is more effective than sleeve gastrectomy in improving short- and mid-term glycaemic control in patients with type 2 diabetes. The outcomes of new surgical interventions (ileal interposition in combination with sleeve gastrectomy (SG) and SG + transit bipartition procedures, etc.) are still insufficient for routine use, and long-term outcomes remain lacking. When and what method to use for which patient will be clarified by future studies.

Keywords: Type 2 diabetes mellitus (T2DM); metabolic surgery; glucose metabolism; insulin resistance (IR); gastrointestinal hormones

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The prevalence of obesity is increasing all over the world. It has become one of the major public health problems due to its comorbidities and negative impact on the quality of life and life expectancy. According to the data of the World Health Organization, the worldwide incidence of obesity has tripled since 1975 (5%). In 2016, it was found that 1.9 billion adults were overweight (39%) and 650 million people (13%) were obese and the rate of those with a body mass index (BMI) of >35 was 4% and with a BMI of >40 was 1%. Obesity is the most well-known risk factor for type 2 diabetes mellitus (T2DM), and T2DM affects more than 400 million people, which is estimated to be around 650 million by 2040 (1,2). A study conducted in Turkey at 2012 found the conducted in Turkey found the prevalence of T2DM as 8% (3). Despite the drugs developed and lifestyle interventions, a significant portion of these patients are unable to achieve their treatment goals. Today, developing more effective treatment modalities for T2DM is on the list of top priorities.

The surgical methods used for obesity have been found to have positive effects on human metabolism beyond weight loss. The information obtained has shown that these methods are an important treatment alternative for T2DM patients. Because of these effects, the concept of "Metabolic

Table 1 Indications for metabolic surgery according to the guidelines of international society

Metabolic surgery should be a recommended option to treat T2DM in appropriate surgical candidates with BMI ≥40 kg/m^2 regardless of the level of glycemic control
Metabolic surgery should be a recommended option to treat T2DM in patients with BMI 35.0–39.9 kg/m^2 within inadequately controlled hyperglycemia despite lifestyle and optimal medical treatment
Metabolic surgery should also be considered to be option to treat T2DM in patients with BMI 30.0–34.9 kg/m^2 and inadequately controlled hyperglycemia despite optimal medical treatment

Surgery" has been defined as "*the manipulation of a normal organ or organ system to achieve a potential health gain*" and used in addition to bariatric surgery (4,5). The current widely accepted indications for metabolic surgery are shown in *Table 1*. In addition to the classical indications for bariatric surgery, patients with uncontrolled diabetes and a BMI of 30–35 have been indicated to be a candidate for such surgeries. These indications are based on observation of the positive effects of alterations in the gastrointestinal tract following bariatric surgical procedures on glucose balance independent of weight loss (6). Both experimental and clinical studies in this respect have led to significant changes in the pathogenesis and treatment of T2DM. This article will summarize the relationship between glucose metabolism, obesity and T2DM, the effects of metabolic surgery on the gastrointestinal system (GIS) physiology, and the results of clinical studies.

Gastrointestinal physiology and glucose metabolism

Circulating glucose is primarily derived from complex carbohydrates taken with foods. It is also derived from precursors such as lactate, pyruvate, amino acids and glycerol via gluconeogenesis. Blood glucose levels are maintained in a narrow range by a number of mechanisms, including the small intestine.

Gastric emptying is regulated by the passage of gastric fluid to the duodenum by opening and closing of the pylorus in relation to blood glucose levels after food intake. Hyperglycemia slows gastric emptying, while hypoglycemia accelerates it. In addition, the duodenogastric feedback mechanism, vagovagal reflex, and GIS hormones are also involved in the regulation of gastric emptying. The enterocytes, which constitute the most important cell group of the small intestine epithelium, are the group of cells that have specific tasks and play a role in food absorption. When the amount of glucose in the intestinal lumen increases, the expression of the receptors, called sodium/glucose cotransporter 1 (SGLT1), which provide the absorption of glucose in the area from the duodenum to the ileum, increases. The increase in glucose absorption through this receptor increases the release of glucagon-like polypeptide (GLP-1) from L cells and gastric inhibitory polypeptide (GIP) from K cells. When glucose enters the enterocyte, it immediately passes to the interstitial space via basolateral glucose transporter (GLUT 2). This two-way transition is dependent on the glucose concentration in the enterocytes. An increase in glucose concentration in the enterocytes reduces hepatic gluconeogenesis. This mechanism is mainly regulated by the ventromedial hypothalamus where insulin receptors are present (7-9).

Glucose metabolism and gastrointestinal physiology are significantly affected by the GIS hormones secreted by enteroendocrine cells, at least 20 different subtypes of which have been found. The effects of these hormones on the normal intestinal tract and their alterations following metabolic surgery will be discussed in the following sections.

Insulin resistance (IR) and diabetes development

IR underlies obesity, T2DM, and cardiovascular diseases. IR is characterized by higher levels of glucose than its storage and use capacity in muscular tissue and an increase in gluconeogenesis in the liver. The majority of obese individuals with IR do not develop hyperglycemia since pancreatic beta (β) cells secrete more insulin to balance blood sugar. However, the continuation of excess glucose intake and the impairment of glucose tolerance in this process result in T2DM development. The studies have shown that hepatic IR is more important than muscle IR in the development of hyperglycemia. Excessive caloric load causes fat accumulation in the liver and fat accumulation causes the development of hepatic IR. The development of hepatic IR inhibits the suppressive effect of insulin on hepatic gluconeogenesis. Increased levels of glucose further increase basal insulin secretion. This results in a

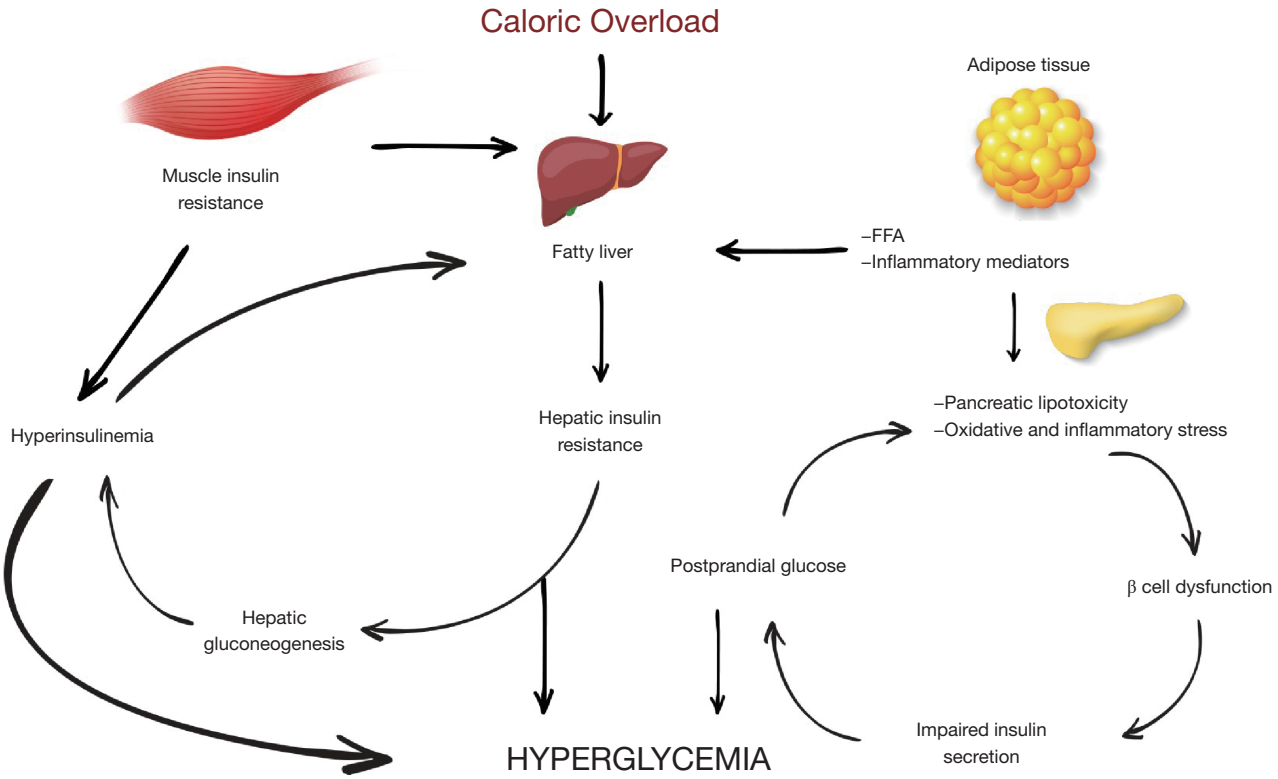

Figure 1 The overview of insulin resistance pathophysiology due to caloric overload.

further increase in fat accumulation in the liver. This fatty liver and an excess of free fatty acids (FFA) disrupt acute insulin release by acting on β cells. Hyperglycemia causes more insulin secretion, increased hepatic lipogenesis, and lipotoxicity in pancreatic β cells. The development of T2DM from the fatty liver is a 2–3-year process. If not reversed, permanent damage occurs in β cells (10,11).

Another problem caused by overeating is that the stimuli from the intestinal system increase the fasting insulin level. Continuously elevated basal insulin level causes the muscle tissue to take up more glucose than it needs or can store. Glucose in the muscle tissue is first converted into pyruvate and subsequently to lactate and alanine. These metabolites are glucogenic substrates and increase the formation of hepatic glucose when they reach the liver (Cori cycle) (12).

Continuous hyperglycemia and increased FFAs from adipose tissue lead to low-grade persistent inflammation and oxidative stress in β cells. FFAs have an anti-insulin function that occurs during lipid metabolism. They increase hepatic gluconeogenesis and fat storage in muscles. Excessive release of FFA, adiponectins, and cytokines such as TNF-α and IL-6 that have destructive effects on β cells and increase apoptosis from adipose tissue into circulation significantly affects metabolism (13).

The development mechanisms of IR and T2DM are shown in *Figure 1*.

Gastrointestinal physiology, hormone changes and glucose metabolism after metabolic surgery

Some of the positive effects of metabolic surgery on blood glucose are undoubtedly caused by weight loss. A significant improvement has been observed in fasting glucose and first-phase insulin release of diabetic patients who underwent severe caloric restriction. However, the improvements in glucose metabolism, especially after Roux-en-Y gastric bypass (RYGB), are too positive that cannot be explained solely by weight loss. It starts in the earlier period, independent of weight loss (14).

In a normal gastrointestinal tract, food digestion and absorption are under the nervous system and hormonal effects. GIS hormones have significant effects on appetite, satiety, and food passage (cephalic, gastric and intestinal phase). These hormones are basically divided into two

as incretins and anti-incretins in terms of their effects on insulin metabolism. After metabolic surgery, an increase has been observed in the levels of hormones with such effects, such as peptide YY (PYY), GLP-1, cholecystokinin, and GIP (15). After RYGB, gastric emptying accelerates for liquid foods, while it slows down for solid foods. Rapid gastric emptying and increased intestinal transit time are correlated with enteroglucagon and GLP-1 levels and weight loss. Because of partial resection of the antrum after sleeve gastrectomy (SG), the emptying of both solid and liquid foods increases. No change has been observed in the emptying of semi-solid food in SG cases where the antrum has been preserved. The rapid passage of food into the intestinal tract increases the release of GIS hormones (11,16). With the effect of hormones, weight loss increases and glucose balance improves. Both GLP-1 and insulin levels have been observed to decrease when food was delivered via a gastrostomy tube placed in the bypassed stomach after RYGB. When foods reach the ileum, a negative feedback occurs from distal to proximal, affecting jejunal motility, intestinal transit time, gastric emptying and pancreatic secretions. This is defined as the "ileal brake mechanism" and is mainly caused by GLP-1. It is not exactly known how this mechanism changes after metabolic surgery (17).

GLP-1 and GIP are two main incretin hormones that increase glucose-stimulated insulin secretion. There is not much research on GIP due to its release in very low amounts, glucagon release, and its less effect on eating behavior and appetite. On the other hand, GLP-1 is an anorexigenic and glucose metabolism regulator, which is located in the distal ileum and colon and released from intestinal L cells and the nucleus tractus solitarius in the brain. It has effects such as glucose-dependent insulin secretion, insulin synthesis, β-cell proliferation, cardioprotection, neuroprotection, satiety. It also reduces hepatic glucose uptake, β-cell apoptosis, glucagon secretion, and gastric emptying rate. Slower passage of food into the intestinal tract improves glucose balance. Intravenous administration of glucose affects GLP-1 levels very little and they are mainly affected by intestinal concentration. A significant increase is seen in its postprandial levels after metabolic surgery. The reason for this increase is explained by the passage of large amounts of food into the ileum due to the anatomical alteration (hindgut hypothesis) (18). Today, its agonists are used in the medical treatment of diabetes and obesity. GLP-1 exhibits its effects on appetite centrally by interacting with vagal afferent nerve fibers (7). After RYGB, GLP-1 levels have been found to be higher in those who succeeded in weight loss in the first year and lower in those who failed (19).

The alternative hypothesis is the foregut hypothesis. As a result of bypassing the upper intestinal tract, the decreased overstimulation with the interruption of the contact of foods with the duodenum and proximal jejunum probably causes the inactivation of anti-incretin factors. Thus, relatively excess incretin hormones increase the activity of insulin and produce positive effects on glucose metabolism. This hypothesis has been proposed with the observation of positive changes in the glucose metabolism of rats that underwent duodenal-jejunal bypass without creating any restriction in the stomach in experimental studies. However, it has not been clearly demonstrated (20).

Metabolic surgical interventions have different effects on insulin. Although fasting insulin levels have been shown to decrease after sleeve gastrectomy, the effects of RYGB surgery are more prominent in this regard. It has been shown that insulin sensitivity increases and the functions of β cell improve. These improvements are seen in the first weeks and are thought to be caused by GLP-1 increase (21).

Ghrelin, on the other hand, is a hormone that has an appetizing effect, suppresses insulin secretion and increases IR. Ghrelin levels increase with prolonged fasting and decrease postprandially. In general, its levels are reported to increase in those losing weight with calorie restriction and it is held responsible for the difficulty in long-term control of diet-induced weight loss. The long-term and short-term effects of metabolic surgery on ghrelin have not been completely clarified. After RYGB, a decrease has generally been observed in its levels. However, some studies have shown increased or normal levels. Although its levels decrease in the first months after surgeries such as RYGB and biliopancreatic diversion (BPD), an increase is observed in its levels in the first year. However, its levels decrease since the fundus where it is secreted most is removed after SG, which is kept responsible for the anti-diabetic effect of SG (22,23).

Changes in bile acid metabolism

Bile acids (BA) have important effects on glucose and lipid metabolism. They inhibit gluconeogenesis via membrane receptors in the ileum and liver (FXR and TGR5) and increase the activation of insulin signaling and glycogen synthesis. They stimulate the formation of postprandial fibroblast growth factor 19 (FGF19) in the ileum, increasing

glycogen synthesis and reducing gluconeogenesis. Activation of these receptors increases GLP-1 release (24). While serum BA levels have been found to be increased after RYGB and SG, this effect could not be demonstrated after gastric band (GB). The most important cause of this increase is considered to be that BAs rapidly reach the distal ileum where FGF-1- and GLP-1-secreting cells are abundantly found. However, the results obtained are variable. There are studies showing a significant increase in serum SA levels within days, while there are also studies showing a significant increase in the first year after surgery (25). Some of the positive effects of metabolic surgical interventions causing changes in the GIS on glucose metabolism are considered to be caused by BA metabolism.

Microbiota

The bacterial structure of the intestinal tract is very complex and reaches very high numbers (10^{12}/gram), especially in the distal ileum and colon. It is mainly composed of Bacteroidetes and Firmicutes groups. It has effects on BA metabolism, intestinal permeability, and inflammation modulation. Anaerobic bacteria convert primary BA into secondary BAs. Secondary BAs bind to TGR5 receptors, producing a positive effect on glucose balance and energy expenditure. The use of BA sequestrants in diabetic patients improves glycemic control. Intestinal bacteria ferment carbohydrates and turn them into short-chain FAs, a source for gluconeogenesis and lipogenesis. Short-chain FAs are also a factor for gut-brain signaling that affects the secretory and absorptive capacities of intestinal epithelial cells. There are not many studies on microbiota changes after metabolic surgery. An increase in *Gammaproteobacteria* and a decrease in Firmicutes have been found. Probiotic diet after RYGB increases weight loss in the early period (26). There is a need for further studies on microbiota change after metabolic surgery and its actual role.

Changes in the GIS after metabolic surgical procedures and their effects on glucose metabolism are shown in *Figure 2*.

Clinical study results

Numerous studies have been conducted on the metabolic effects of bariatric surgery. Almost all of the studies have shown a significant improvement in T2DM patients. The definitions of remission, improvement and worsening after metabolic surgery vary. While a fasting blood glucose (FBG) level of <1.10 g/L or an HbA_{1c} of <6.5% for at least 1 year without treatment is generally considered as remission criterion, the American Diabetes Association (ADA) criteria for remission are more rigid and are considered as an HbA_{1c} of <5.7% a glucose level of <5.6 mmol/dL. An HbA_{1c} of <6.4% and a glucose level of <6.0 mmol/L are considered as partial remission (6). The criteria used when evaluating the results of the studies are important in the analysis of numbers (27,28).

In the meta-analysis of Buchwald *et al.* published in 2004, the rate of T2DM remission after bariatric surgery was found as 48% for GB, 72% for RYGB, 84% for BPD and 99% for duodenal switch. In this study, patients who achieved normal glucose levels without using medical treatment were considered as cured (29). In the Swedish Obese Subjects (SOS) study, an observational study, the outcomes of the surgical group and non-surgical group with indications were compared. During the 2-year follow-up, the rates of T2DM remission were 76% in the surgical group and 16% in the non-surgical group. In the 15-year follow-ups, the rates were 30.4% and 6.3%. In the 15-year follow-ups of patients with prediabetes at baseline, diabetes became prominent in 15.6% of patients in the surgical group and 54.5% of patients in the control group (30). In a meta-analysis of 6,373 patients analyzing twenty-one cohort studies, the two-year remission rate was 65%. The remission rate was 99% for BPD, 74% for RYGB, 61% for SG, and 33% for GB procedure (31). In another meta-analysis analyzing randomized controlled studies comparing metabolic surgery and medical treatment-follow-up, the efficacy of metabolic surgery in achieving remission was far superior to the medical group (RR: 22.1; P=0.002) (32). Hayoz *et al.* published a systematic review and meta-analysis of randomised controlled trials comparing the effects of RYGB with those of SG on metabolic outcome, with a special focus on glycaemic control. Based on their meta-analysis results, RYGB is more effective than SG in improving weight loss and short- and mid-term glycaemic and lipid metabolism control in patients with and without T2DM. They concluded that RYGB should be the first choice to treat patients with obesity and T2DM and/or dyslipidaemia (33). Despite some fictional differences in the studies conducted in this respect, the superiority of metabolic surgery is obvious.

In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study, 150 T2DM patients with a BMI value ranging from 27

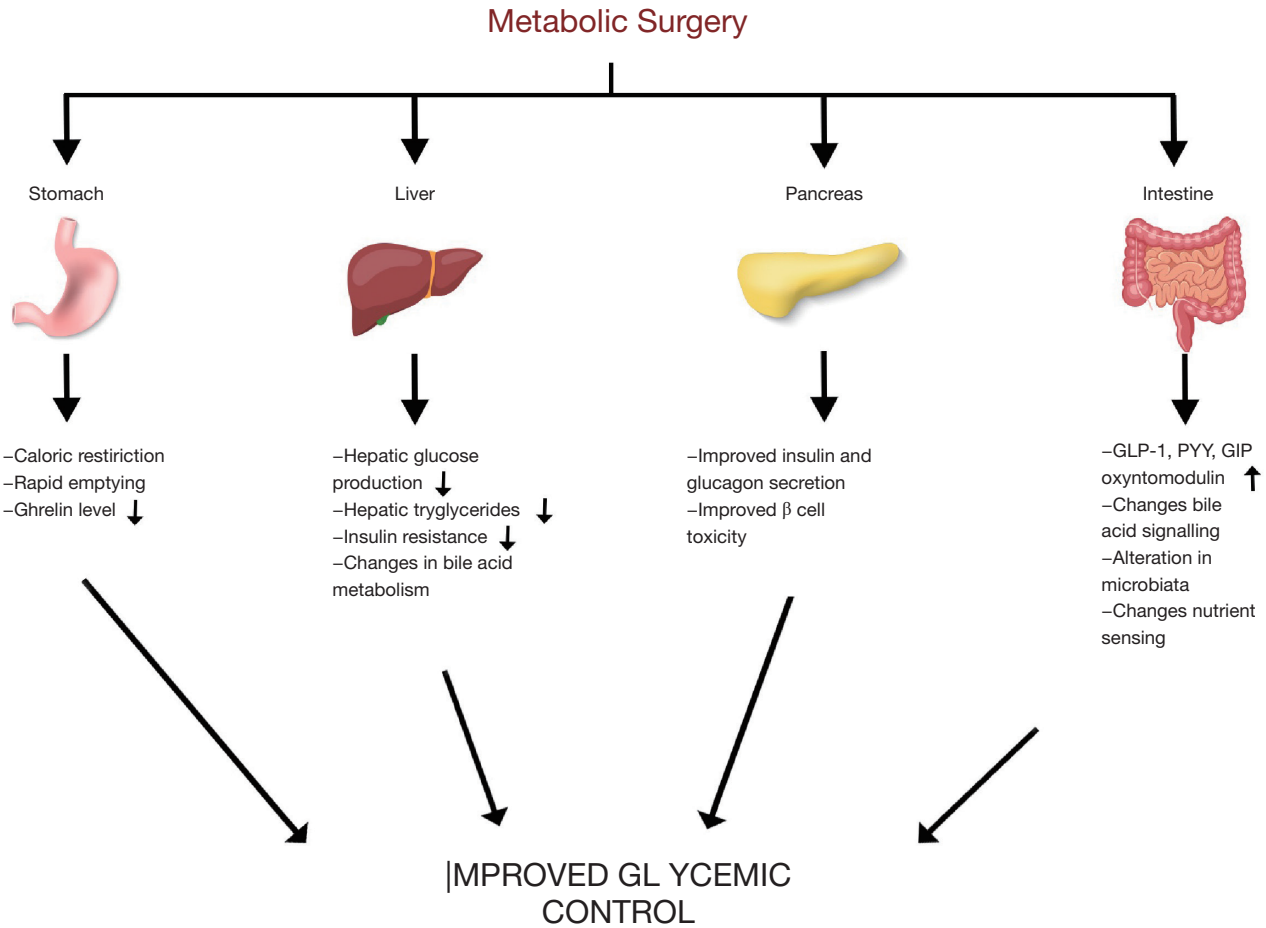

Figure 2 The effects on glucose metabolism of metabolic surgery.

to 43 BMI were randomized to RYGB, SG, and intensive medical treatment. In the one-year follow-up, the remission rate was 12% in the medical treatment group, while it was 37% in the SG group and 42% in the RYGB group. In the 3-year follow-up, these rates were 5%, 24%, and 38%, respectively. The five-year results were obtained from 134 patients, and the remission rates were 5% in the medical group, 23% in the SG group, and 29% in the RYGB group. Similar results were also observed in terms of weight loss, quality of life and lipid levels (34-36). In the meta-analysis of Sheng *et al.* investigating T2DM remission, microvascular and macrovascular complications of bariatric surgery with at least five years of follow-up, the remission rate was found to have increased significantly (65% *vs.* 15.6%, RR: 5.90). There was a 79% decrease in microvascular complications (RR: 0.37) and a 48% decrease in macrovascular complications (RR: 0.52) and the mortality rate was 79% (RR: 0.21) lower than that of the medical treatment group (37). The study by Mingrone *et al.* compared medical treatment, RYGB and BPD in 60 patients with a BMI of >35 compared and found remission rates to be 75% for RYGB, 95% for BPD, and 0% for medical treatment in the two-year follow-up (38). In the meta-analysis of Panunzi *et al.* including 94,579 patients, no difference was found between the patients with a BMI of <35 and those with a BMI of >35 in terms of diabetes remission (71% *vs.* 72%) (39). Similar results were also obtained in the meta-analysis of Cummings *et al.* analyzing 11 randomized controlled studies (40). Despite the quite positive outcomes of metabolic surgery, the absence of adequate response in about 30% of patients suggests the need for good patient selection and information. There was no relationship between inadequate weight loss and response in the unresponsive patient group. Advanced age, long-term disease, polypharmacy and high HbA1c levels are important factors in failure of glycemic control after

Table 2 The results of randomized controlled trials for metabolic surgery *vs.* medical treatment

Author	Intervention (*vs.* medical)	BMI (kg/m^2)	Sample size	Follow-up duration	Remission rate (%)
Schauer *et al.* (34-36)	RYGB-SG	27–43	150	1 yrs	42 *vs.* 37 *vs.* 5
				3 yrs	38 *vs.* 24 *vs.* 5
				5 yrs	29 *vs.* 23 *vs.* 6
Mingrone *et al.* (38)	RYGB-BPD	≥35	60	2 yrs	75 *vs.* 95 *vs.* 0
Dixon *et al.* (43)	GB	30–40	60	2 yrs	73 *vs.* 13
Liang *et al.* (44)	RYGB	>28	108	1 yrs	90 *vs.* 0
Wentworth *et al.* (45)	GB	25–30	51	2 yrs	52 *vs.* 8
Ikramuddin *et al.* (46)	RYGB	30–39.9	120	1 yrs	49 *vs.* 19
Courcoulas *et al.* (47)	RYGB-GB	30–40	69	1 yrs	17 *vs.* 23 *vs.* 0
Simonson *et al.* (48)	RYGB	30–42	38	3 yrs	42 *vs.* 0
Parikh *et al.* (49)	RYGB-SG-GB	30–35	57	6 months	65 *vs.* 0
Horwitz *et al.* (50)				3 yrs	63 *vs.* 0
Ding *et al.* (51)	GB	30–42	45	1 yrs	33 *vs.* 23
Cummings *et al.* (52)	RYGB	30–45	43	1 yrs	60 *vs.* 6

surgery (41,42).

The results of randomized controlled studies are shown in *Table 2* (34-36,38,43-52).

The choice of surgical method is another topic of discussion in this field. Metabolic activity is ranked as BPD > RYGB > SG > GB. For now, the most commonly performed metabolic surgery and the most widely accepted metabolic surgical intervention by the guidelines are RYGB, BPD and their modifications (53). The results of some new methods are also published.

New surgical interventions

In addition to interventions in the guidelines as the standard for metabolic surgical procedures, there are various studies and results on ileal interposition in combination with SG and SG + transit bipartition procedures. The first studies on ileal interposition were conducted by DePaula *et al.* on a group of 69 patients. In this study with a mean follow-up period of 21.7 months, the rate of patients with an HBA1c of <6 was reported to be 65.2% (54). In a study of 120 patients published by the same team in 2011, the remission rate was found as 84.2% (55). In a study of 30 patients published by Foschi *et al.* in 2019 comparing ileal interposition with standard medical treatment, the rate of 5-year complete T2DM remission was found as 68% (56). Transit bipartition was first proposed by Santoro in 2012 for metabolic syndrome with a remission rate of 86% (57). In a case series study by Yormaz *et al.* comparing ileal interposition, transit bipartition, and sleeve gastrectomy, the one-year remission was reported as 35.3%, 67.9%, and 54.7%, respectively (58). Although such surgical procedures are performed quite often in practice, both the number of cases in the published series is low and long-term results are insufficient. The initial remission rates obtained were close to RYGB outcomes and lower than BPD outcomes. However, the outcomes of such surgical interventions are still insufficient for routine use, and long-term outcomes remain lacking. Therefore, these procedures should be performed only within the study protocols.

Conclusions

Today, metabolic surgery is the only treatment modality that has the most positive and long-lasting effect on T2DM remission. Small intestines play a primary role in glucose balance with many mechanisms. These physiological effects are enhanced by some changes made in bariatric surgery. Metabolic surgical methods affect morphology, endocrine functions and digestive system physiology. Although a significant portion of its effects is related to weight loss, rapid changes in GIS hormones are particularly responsible

for early metabolic effects. They show their effects with increased incretin hormone levels, decreased anti-incretin hormone levels, central effect through the vagus, change in bile acid metabolism, GIS microbiota change.

The clinical studies have confirmed these effects and therefore the indications for metabolic surgery have expanded. The standard recommended methods for metabolic surgery include SG, RYGB and BPD and their modifications. When and what method to use for which patient will be clarified by future studies. There is a need for studies with larger sample size and long-term results for the new methods to be used in daily practice.

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Footnote

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