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ABOUT COVER

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REVIEW

Progress in treatment of type 2 diabetes by bariatric surgery

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Abstract

The incidence of type 2 diabetes (T2D) is increasing at an alarming rate worldwide. Bariatric surgical procedures, such as the vertical sleeve gastrectomy and Roux-en-Y gastric bypass, are the most efficient approaches to obtain substantial and durable remission of T2D. The benefits of bariatric surgery are realized through the consequent increased satiety and alterations in gastrointestinal hormones, bile acids, and the intestinal microbiota. A comprehensive understanding of the mechanisms by which various bariatric surgical procedures exert their benefits on T2D could contribute to the design of better non-surgical treatments for T2D. In this review, we describe the classification and evolution of bariatric surgery and explore the multiple mechanisms underlying the effect of bariatric surgery on insulin resistance. Based upon our summarization of the current knowledge on the underlying mechanisms, we speculate that the gut might act as a new target for improving T2D. Our ultimate goal with this review is to provide a better understanding of T2D pathophysiology in order to support development of T2D treatments that are less invasive and more scalable.

Key Words: Obesity; Bariatric surgery; Type 2 diabetes; Insulin resistance; Bile acids; Microbiota

Core Tip: Bariatric surgery is an effective treatment for type 2 diabetes (T2D), providing long-term remission. Among these types of weight loss procedures, the vertical sleeve gastrectomy and Roux-en-Y gastric bypass are extensively performed worldwide, but in the United States especially. Through establishment of reduced caloric intake and alterations in gut hormones, bile acids, and intestinal microbes, these procedures also contribute to the resolution of T2D. Understanding the mechanisms

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underlying the effects of bariatric surgery on T2D might provide new targets for more effective non-surgical treatments, such as medications, for T2D.

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INTRODUCTION

Obesity is a chronic disease, affecting individuals throughout the world and steadily escalating[1,2]. Indeed, the incidence of obesity has more than doubled from 1975 (at 5%) to 2014 (at 13%)[3,4]. According to this trend, the number of obese people may account for as many as one-fifth of the world's population in the recent upcoming years. Obesity is an important risk for type 2 diabetes (T2D)[3], and as such the alarming rise in obesity has been accompanied by an expanding burden of T2D. At present, the prevalence of T2D stands at 9% worldwide, but it is predicted to reach approximately 12% by 2025 if trends continue[5], making it imperative to address the problem of obesity and T2D.

Although nonsurgical intervention can lead to weight reduction and concomitant improvement of T2D, the magnitude is modest and the benefits are not durable[6,7]. Bariatric surgeries, such as the vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) procedures, have proven to be the most efficient treatment for obesity and T2D[8-11]. Moreover, compared to the currently available nonsurgical interventions, bariatric surgery yields better outcomes for glycemic control and remission of T2D[7,8,12,13]. Yet, weight loss alone is not the key mechanism by which these surgical procedures imperatively improve T2D. Understanding the molecular underpinnings of these procedures is paramount, as they are now heavily employed in the treatment for diabetes.

The purpose of this review is to summarize the recent advances in this field and highlight the mechanisms by which bariatric surgeries benefit diabetic patients. Here, we describe contemporary bariatric surgery procedures and their beneficial effects on T2D, and discuss the implication of each on future research to improve the treatment of T2D, particularly for future nonsurgical approaches.

EVOLUTION OF BARIATRIC SURGERY

Despite bariatric surgery having been originally developed in the 1950s, the annual number of bariatric surgeries performed worldwide remains relatively low. In 2019, 833678 operations were reported (according to the International Federation for Surgery of Obesity Global Registry data)[14,15]. It is worth noting that this global number represents less than 1% of the overall eligible population with morbid obesity; as such, the potential for greater application of bariatric surgery is very large. During the period from 2010 to 2018, the proportion of RYGB procedures actually decreased (from 55% to 17%), as did that of the adjustable gastric banding (AGB) procedure (from 40% to 5%-10%)[14]. By comparison, the proportion of VSG procedures rose substantially (from 2% to 61%)[14]. The biliopancreatic diversion (BPD) procedure currently accounts for approximately 1% of the overall bariatric surgeries performed[16]. Thus, the most commonly performed bariatric surgery worldwide is VSG, followed by RYGB. In terms of the T2D remission outcome, it remains unknown whether any difference exists between the two most prevalent procedures and the underlying mechanisms of both procedures remain to be fully elucidated.

CLASSIFICATION OF BARIATRIC SURGERY PROCEDURES

In line with the direct surgical effects on food intake and/or nutrient absorption, bariatric surgical procedures are traditionally classified as restrictive, malabsorptive,

or mixed operations. The restrictive-type techniques, including AGB, VSG, and vertical banded gastroplasty, physically decrease the size of the stomach in order to trigger earlier satiety during meals. The malabsorptive-type techniques, such as BPD, establish a bypass of the partial small bowel in order to induce bile acids (BAs) and food to be mixed in the distal 50-100 cm of the ileum, thereby prompting macronutrient malabsorption. The mixed-type procedures, such as RYGB, combine physical reduction of the stomach volume with a bowel bypass[17]. Due to the overall advancements in surgical techniques and greater knowledge gained through related clinical research, several novel bariatric surgical procedures have been introduced; these include the ileal interposition and duodenal-jejunal bypass. However, VSG and RYGB still account for the majority of weight-loss surgeries performed internationally. Given that any reconfiguration of the gastrointestinal tract involves a complex operation, classifying the modalities of such procedures into restrictive, mal-absorption, or mixed is too simplistic; gaining a definitive understanding of the outcomes of the different bariatric operations will facilitate the most accurate application of each to achieve maximal benefit.

SURGICAL PROCEDURES

AGB

In AGB, a silicone ring is placed to encircle the upper region of the stomach and form a high-pressure zone above the gastric band, creating a small gastric pouch. The size of the gastric band itself can be adjusted by injection of sterile saline or air in a subcutaneous port. The goal of this approach is to decrease hunger and consequent caloric consumption[18,19].

Unfortunately, AGB has several risks and undesirable side effects; for example, it increases the risk of gastroesophageal reflux and is associated with a risk of band erosion[20]. Its benefits on weight loss are also relatively short-term. Thus, the prevalence of this technique has declined, both in the United States (where it enjoyed a particular popularity) and worldwide[21-24]. The rates of AGB impacts on weight loss and subsequent resolution of T2D remain appreciably below 50%, with 34% of patients experiencing excessive weight loss and 33% of patients achieving remission of T2D at 1 year[25] (Table 1).

RYGB

In RYGB, the stomach is transected along the lesser curvature to create a small gastric pouch (10-30 mL volume), which is anastomosed to the segment of the intestinal division to create an alimentary limb (75-100 cm length) following transection of the jejunum, without exposure to biliopancreatic secretion[26]. The stomach remnant is left *in situ* and in continuity with the duodenal and proximal jejunum, forming a biliopancreatic limb that contains only digestive enzymes and preventing direct contact with chyme. Following transection of the jejunum, the restoration of intestinal continuity occurs *via* a structuring of the proximal stump of the small bowel that is anastomosed to the alimentary limb to create a common limb, where the chyme is then allowed to contact the digestive enzymes and go through the processes of digestion and absorption.

The surgical realignment of the gastrointestinal tract represents not only a profound anatomic alteration but a physiological one as well, changing the profiles of BAs, gut hormones, and even the gut microbiota. Contingent upon the patient's body mass index (BMI) and/or severity of T2D, the extension of the alimentary limb length can contribute to a better weight reduction and more notable remission of T2D[27], although it is also accompanied by an increased risk of nutrient deficiency and other complications, like urolithiasis. The effect of RYGB on T2D has been reported to have remission rates of 60%[28] and 75%[29] after 1 and 2 years, respectively (Table 1), which are similar to those of VSG[30].

VSG

In VSG, along the great curvature transecting 70%-80% of stomach, the remnant stomach remains as a tubular structure. During the meal, then, the tubular stomach is short of accommodative ability and enhances gastric emptying[31-34].

Over the last decade, VSG has been performed as a single-stage procedure. Given the maintenance of the native food passage and the reduction of gastric volume, VSG markedly diminishes the risk of nutrient deficiency. Its relative simplicity and good clinical outcomes have allowed VSG to surpass RYGB in recent years as the most

Table 1 Randomized controlled trials of bariatric surgery *vs* medical treatment for type 2 diabetes

Ref.	Intervention	Control	Follow-up in mo	Diabetes remission, surgery *vs* control (%)
Parikh *et al*[30], 2014	VSG	Medication	6	65 *vs* 0
Simonson *et al*[25], 2019	AGB	Medication	12	33 *vs* 23
Cummings *et al*[28], 2016	RYGB	Medication	12	60 *vs* 6
Mingrone *et al*[29], 2015	BPD; RYGB	Medication	24	95 *vs* 0; 75 *vs* 0

AGB: Adjustable gastric banding; BPD: Biliopancreatic diversion; RYGB: Roux-en-Y gastric bypass; VSG: Vertical sleeve gastrectomy.

prevalent weight-loss surgery in the United States and worldwide[35]. On account of the mechanical removal of the great curvature, gastric hormone levels become markedly altered, the most obvious of which being the secretion of ghrelin, a hunger hormone produced by the X/A-like cells in the fundus of the stomach. However, the levels of secreted peptide-YY (PYY), which controls the blood glucose concentration, become increased. The rate of T2D resolution after VSG has been reported as 65%[30] (Table 1).

BPD

BPD consists of two distinct stages, namely, creation of a tubular gastric pouch and an intestinal bypass. The VSG is conducted *via* removal of approximately 80% of the stomach, after which most of the small bowel is bypassed, leading to malabsorption. The duodenum is divided at the first portion, followed by transection of a segment of the distal ileum (at 250 cm proximal to the ileocecal valve) and anastomosis to the proximal end of the divided duodenum. Intestinal continuity is restored by the ileoileostomy, at 100 cm proximal to the ileocecal valve.

Unlike other procedures, BPD not only decreases caloric consumption but also leads to malabsorption of some nutrients and vitamins. Owing to the malabsorption resulting from the bypass of the major portion of the bowel, BPD is considered the most effective bariatric surgery for severe obesity and T2D. A randomized trial showed that BPD leads to a 70% excessive weight loss by the 2-year follow-up and more than 90% resolution rate of T2D compared to conventional medical therapy[29]. Nonetheless, because of the technical complexity and associated complications, such as nutritional deficiency, compared with RYGB and VSG, the use of BPD has been declining year by year[36]. At present, BPD is mainly applied to treat patients whose BMI is greater than 50 kg/m^2 or who have refractory T2D[12,13,29]. The 2-year diabetes remission rate after BPD is 95%, representing the highest remission rate of all bariatric surgeries[29] (Table 1).

Control of T2D by bariatric surgery

Although bariatric surgery confers the potent ability to the remission of T2D, it is only indicated for obese diabetic patients (BMI > 35 kg/m^2). The pathogenesis of T2D is mainly attributable to insulin resistance and impairment of β-cell function[37]. Plenty of studies have investigated the mechanisms by which bariatric procedures might result in T2D remission *via* increase of insulin sensitivity and/or β cell function[38-40]. The resolution of T2D after bariatric procedures was traditionally thought to be the result of decreased caloric consumption, weight loss, and nutritional malabsorption; however, the remission of diabetes occurs sooner than the surgery-induced weight loss [41,42]. Emerging evidence supports the hypothesis that bariatric procedures remit T2D *via* mechanisms that are independent of weight reduction[11,43-45]. Thus, investigations of the alterations in the gastrointestinal tract, either anatomical or physiological, will help to provide a better understanding of the effect of bariatric surgery on T2D[46-48].

Lipid metabolism

Multiple mechanisms result in defective insulin secretion and response in T2D, such as lipotoxicity, oxidative stress, and endoplasmic reticulum (ER) stress[49]. The majority of patients with severe obesity present some dyslipidemia, such as hyperlipemia and lipoprotein abnormality, which cause excessive fat deposition in important tissues and/or organs, including adipose tissue and the liver, muscle, and pancreas. The excess accumulation of fat in the body induces chronic tissue inflammation and consequent tissue insulin insensitivity, which is a well-described feature of obese

diabetic patients[50]. Thereby, the mechanism that accelerates the improvement of hyperlipemia may improve tissues and/or organs functions and insulin sensitivity, and eventually leads to remission of T2D. Evidence is expanding that bariatric surgery produces marked improvement in dyslipidemia[51,52]. However, there are some differences in clinical effectiveness on dyslipidemia, possibly due to variance in each surgical anatomy. Taken together, the improvement of dyslipidemia metabolism after bariatric surgery may contribute to the attenuated insulin resistance and resolution of T2D, but the molecular mechanism warrants further investigation.

POTENTIAL MECHANISMS OF IMPROVEMENT OF T2D

Gastrointestinal hormones

Ghrelin: Ghrelin, an appetite-stimulating hormone mainly secreted from gastric X/A-like cells (PD/1 cells in human), regulates peripheral glucose homeostasis in a pattern that decreases glucose-stimulated insulin release[53,54] and promotes insulin resistance in muscle[55], in addition to increased food intake[56,57]. In particular for VSG, the removal of the gastric fundus markedly blocks the major source of ghrelin. Thus, inhibition of ghrelin production seems to be a plausible explanation for the observed improved glycemia. Accumulating evidence shows that circulating ghrelin is decreased after VSG, but decreased or not changed at all after RYGB[58-60] (Table 2). Nevertheless, in the VSG mouse model, the glycemic control outcome is similar between ghrelin-deficient and wild-type mice[58]. Altogether, the data suggest that decreased ghrelin cannot completely explain the observed improved glycemic homeostasis after VSG.

Glucagon-like peptide: Glucagon-like peptide (GLP-1), produced from intestinal L cells, activates insulin secretion and reduces glucagon release in a glucose-dependent manner in response to nutrient uptake in the gut[61]. Despite administration at a superphysiological dose, GLP-1 analog only partially improves the incretin effect in patients with T2D[62]. Following both VSG and RYGB, the postprandial level of GLP-1 is markedly increased, implying that GLP-1 acts as an incretin signal contributing to glycemic homeostasis[63,64] (Table 2). Mouse model studies comparing pharmacologic blockade of the GLP-1 receptor and bariatric surgeries, including both VSG and RYGB[65-68], have found similar responses to glycemic control in wild-type mice, suggesting that the action of endogenous GLP-1 does not account for the benefit of those bariatric procedures on T2D.

PYY: PYY, a 36-amino acid peptide, is produced by L cells and expressed in the pancreas and neurons in the central nervous system[69,70]. PYY was first reported in the early 1980s, when it was characterized as playing an important role in promoting gastric and pancreatic secretions and modulating the gastrointestinal tract function. In recent years, expanding evidence has signified that PYY can act on the Y2 receptor to regulate insulin sensitivity and glucose uptake. Moreover, PYY has also been shown to act on pancreatic islets to regulate insulin release. A lack of PYY in the gut and pancreas with reduced β cell mass resulted in insulin secretion disorder[71]. In contrast, overexpression of PYY in islets improved insulin secretion in response to glucose and increased β cell mass[72]. Of note, a large amount of evidence has emerged to indicate that the serum level of PYY is elevated following both VSG and RYGB[73] (Table 2). Therefore, PYY is likely to play a vital role in the bariatric surgery-induced remission of T2D.

BAs

In response to a meal, BAs are secreted by hepatocytes and released into the duodenum. Although it was shown over that past decade that BAs enable micelle formation and stimulate nutrient absorption and emulsification, it is only now becoming clear that BAs serve as signaling molecules in multiple biological responses, including glucose metabolism. Circulating BA levels become increased after bariatric procedures, including both VSG and RYGB, and have been implicated in the regulation of glucose homeostasis (as observed in rodent models and human patients) [74-77] (Table 2). These findings also represent a plausible explanation for the increase in BAs that occurs upon realignment of the gastrointestinal tract by the RYGB technique's exposure of the ileum to chyme that had avoided the digestion process thus far. In line with this notion, when high-fat diet-induced obese rodents were subjected to exposure of the ileum to BAs, they achieved a level of glucose improve-

Table 2 Several factors contributing to improved type 2 diabetes after bariatric surgery

Target	Major site of secretion (anatomical location)	VSG	RYGB
Ghrelin	X/A-like cells (stomach)	Decrease	Decrease or no change
GLP1	L cells (distal gut)	Increase	Increase
PYY	L cells (distal gut)	Increase	Increase
Bile acids	Hepatocytes	Increase	Increase
FGF-15/19	Ileum	Increase	Increase
Microbiota	Gut	Change	Change
Enteroplasticity	Gut	Change	Change

Multiple factors appear to drive the remission of type 2 diabetes after bariatric surgery, including decreased ghrelin, increased glucagon-like peptide, increased peptide-YY, increased bile acids, increased fibroblast growth factor-15/19, and alteration of microbiota and enteroplasticity. Data are derived from both human and animal studies. GLP1: Glucagon-like peptide 1; FGF: Fibroblast growth factor; PYY: Peptide-YY; RYGB: Roux-en-Y gastric bypass; VSG: Vertical sleeve gastrectomy.

ment that was identical to that observed in T2D patients after RYGB, suggesting that BAs may play a pivotal role in the effect of RYGB on glycemic control[78,79]. Intriguingly, an increase in circulating BAs has been found in rodents and humans following VSG, further suggesting that BA profile changes likely represent a physiological modality for T2D remission *via* bariatric surgery.

The increased serum BAs contribute to the improvement of impaired glucose homeostasis mainly through two corresponding signaling pathways, namely, those involving the farnesoid-X receptor (FXR) and the transmembrane G protein-coupled receptor 5 (TGR5)[77,80-83]. Overexpression of FXR in db/db mice improved metabolic disorders, indicating that FXR signaling may serve as a therapeutic target for maintaining metabolic homeostasis[84,85]. BAs function as a ligand for FXR, which can underlie the observed improvement of glucose metabolism *via* the FXR-related pathway. Compared with wild-type mice, mice that are deficient in FXR forfeit the ability to maintain glucose equilibrium following VSG[86]. Furthermore, it was shown that the increase in fibroblast growth factor-15 (FGF19 in human), a downstream effector of the BAs-FXR pathway, after bariatric surgery contributes to hepatic glycogen synthesis and reduces glycemia[87-89].

In contrast to FXR, TGR5, a G protein-coupled receptor, is expressed in multiple tissues, including the intestine, skeletal muscle, liver, and adipose tissue. The increased BAs after VSG confer the ability to remit insulin resistance in a TGR5-activation manner[90,91]. Compared with results from studies in wild-type mice, the improvement of T2D in TGR5$^{-/-}$ mice was severely blunted, suggesting that TGR5 might be essential for glycemic control after VSG[90].

Gut microbiota

Over the past years, the association between the gut microbiota and altered metabolic processes has been recognized in both rodents and humans[92-96]. In addition, a large bacterial population shift has been observed following the bariatric procedures, including VSG and RYGB[97-100] (Table 2). Compared with results in sham operation models, the relative abundance of Gammaproteobacteria (*Escherichia*) and Verrucomicrobia (*Akkermansia*) is rapidly and sustainedly enhanced after RYGB[101]. In concert with this, the shift of the gut microbiota from the RYGB group to germ-free mice leads to a weight reduction, implying that gut microbiota contributes to weight loss[101]. Moreover, allogenic fecal microbiota transplantation using metabolic syndrome donors led to impairment in insulin sensitivity for the metabolic syndrome recipients compared with using post-RYGB donors[102]; this finding indicates that the alteration of intestinal microbes after RYGB can exert a positive effect by improving insulin resistance.

Enteroplasticity

In response to internal and external environmental stimuli, the processes of proliferation, migration, death, and differentiation of epithelial cells take place in the human small intestine[103]. Thereby, enteroplasticity or intestinal adaptation, including

morphological and nervous system alterations, refers to the capacity to adapt functionally, as occurs in diabetes, aging, and so forth[104]. Western diet might contribute to alterations of enteroplasticity that result in metabolic derangement; hence, it is worth exploring whether bariatric surgery might lead to changes in enteroplasticity. Increasing evidence suggests that several bariatric surgical procedures trigger changes of enteroplasticity[105-107] (Table 2). The intestinal morphology, including width and cellular proliferation, was found to be enhanced in the alimentary and common limbs in an RYGB rat model[108,109], and the intestinal villus height and surface area were found to be reduced in mice after VSG[110]. Additionally, some studies indicated that the hepatoportal sensor pathway plays an important role in glycemic control after RYGB, unlike findings after AGB[111]. Altogether, these data signify marked changes in enteroplasticity occurring after bariatric surgery.

CONCLUSION

The escalating pandemic of T2D continues to be a worldwide problem. Through its impressive efficacy, bariatric procedures are still the most effective and efficient durable therapy for the improvement of T2D in severe obesity. Moreover, the outcomes of weight-loss surgery provide novel scientific clues and a theoretical foundation for the gut's potential to act as a therapeutic target for remission and countering of insulin resistance. Taken together, although great progress has been made in our understanding of the mechanisms by which bariatric surgery may improve T2D, the discrepancy of certain evidence is undetermined and requires further research efforts.

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