Bariatric surgery: a cure for diabetes?

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Purpose of review

To review the basic mechanisms of caloric intake reduction of bariatric surgery and its clinical and metabolic outcomes. To describe novel bariatric procedures, their effects on glucose homeostasis and insulin sensitivity and to explain the proposed mechanisms for type 2 diabetes mellitus (T2DM) resolution.

Recent findings

The effects of surgically induced weight loss on T2DM have elucidated in part the role of proximal and distal gastrointestinal bypass on insulin sensitivity. A dual mechanism for improvement in glucose homeostasis after bariatric surgery has been proposed that appears to be weight loss independent.

Summary

Bariatric surgery is the most effective therapy for obesity and obesity-related comorbidities today that provide high rates of resolution of T2DM with improvements in insulin resistance and β-cell function. Novel bariatric procedures offer a unique opportunity to understand the pathophysiology of T2DM and to identify potential pharmacologic targets for effective T2DM treatments and a potential cure.

Keywords

bariatric surgery, glucose homeostasis, insulin resistance, beta cell function, obesity, type 2 diabetes, pancreas burnout

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Introduction

Obesity is associated with increased overall mortality with a known direct correlation between BMI and mortality [1•]. In addition, obesity, glucose intolerance and hypertension in children are strongly associated with increased rates of premature death [2•]. Obesity has been established as an important risk factor for the development of type 2 diabetes mellitus (T2DM), both of which are major public health problems in the USA. Bariatric or weight loss surgery is currently the most effective weight loss therapy for obesity. The term 'Metabolic Surgery' has been adopted by surgical societies to denote the influence of gastrointestinal surgery on metabolism. Roux-en-Y gastric bypass (RYGB), which is the most commonly performed bariatric procedure in the USA, results in resolution of T2DM in approximately 80% of patients. T2DM resolution has been defined by clinical normalization of glucose parameters (i.e. fasting glucose and HgA1c) and discontinuation of all anti-T2DM medications, including insulin. Is it possible that bariatric surgery can cure T2DM? If we call the cure the long-term remission, then the answer is yes. At least, it appears so in the majority of patients. There are several factors involved in the likelihood of remission of T2DM. Furthermore, the mechanisms by which these surgeries provide T2DM resolution are not completely elucidated. What appears evident is that it exists both as weight dependent and independent mechanistic effects on glucose homeostasis after bariatric surgery. In this review, various standard and novel bariatric procedures are available today, their impact on glucose homeostasis and proposed mechanisms are presented.

Bariatric surgery

Bariatric surgery is the most effective long-term treatment known today for severely obese patients [3]. Several gastrointestinal configurations have been created to provide sustained weight loss and long-term improvement in metabolic parameters. The RYGB is the most popular bariatric surgical procedure performed in the USA. [4]. The RYGB procedure is considered the gold standard bariatric procedure to which all bariatric surgeries are compared. RYGB has been performed for almost 50 years and has undergone various modifications over time. In general, all bariatric procedures involve manipulation of the proximal gastrointestinal tract with or without proximal bypass. Typically, obese individuals with a BMI greater than 35 kg/m^2 have been considered candidates for bariatric surgery, if they have obesity-related comorbid conditions including T2DM. In fact, bariatric surgery has been termed 'diabetes surgery' during the first Diabetes Surgery Summit in 2008 [5], because it has been recognized that bariatric surgery is a valuable tool to treat obesity and T2DM [6]. Current research focuses on the discovery of the underlying mechanisms for T2DM resolution after bariatric surgery that may lead to the development of suitable nonsurgical treatments of obesity and T2DM.

Bariatric surgery outcomes

The bariatric surgeries available today provide greater and sustained weight loss and resolution of the majority of obesity-associated comorbidities including T2DM when compared with medically controlled individuals [3,7–10]. Undoubtedly, the combination of restriction and malabsorption during these procedures provide greater weight loss and T2DM resolution rates when compared with their restrictive-only counterparts [11]. In addition, their safety profile varies widely; adjustable gastric banding providing the safest profile of all [12–14]. In addition, bariatric surgery also has been found to decrease overall mortality and cancer incidence in severely obese patients [15,16]. The risk of death and other adverse outcomes after bariatric surgery is low when compared with other commonly performed gastrointestinal surgeries which to date makes bariatric surgery a safe procedure in all age groups [4,17,18].

Standard bariatric surgery

Bariatric surgery involves surgical manipulation of the proximal gastrointestinal tract with or without proximal bypass. These surgeries have various anatomic variations and can provide both restriction and malabsorption of nutrients (Fig. 1). The abandoned vertical-banded gastroplasty (VBG), the most recently established adjustable gastric banding (AGB) and sleeve gastrectomy are typically considered restrictive-only operations. The VBG consists of a proximal gastric partition with restrictive nonadjustable band (Fig. 1a). The AGB is an adjustable band placed just below the gastroesophageal junction (Fig. 1b). The sleeve gastrectomy is a vertical gastrectomy or sleeve that is dependent on the lesser curvature of the stomach. The RYGB (Fig. 1c) and the biliopancreatic diversion (BPD) without (Fig. 1d) or with duodenal switch (Fig. 1e) have both restrictive and malabsorptive components. The RYGB is performed by creating a small gastric pouch with a proximal gastroenterostomy that bypasses the stomach with approximately 100 – 150 cm Roux limb enteroenterostomy. Whereas the BPD involves a partial distal gastrectomy with a proximal gastroenterostomy and a long Roux limb and distal enteroenterostomy located less than100 cm from the ileocecal valve, the duodenal switch modification involves a longitudinal gastrectomy (sleeve gastrectomy) with a proximal duodenoenterostomy and distal enteroenterostomy less than100 cm from the ileocecal valve. All of these bariatric procedures may be performed by laparoscopic or minimally invasive techniques, which has been shown to improve short-term outcomes [19].

> **Key points**
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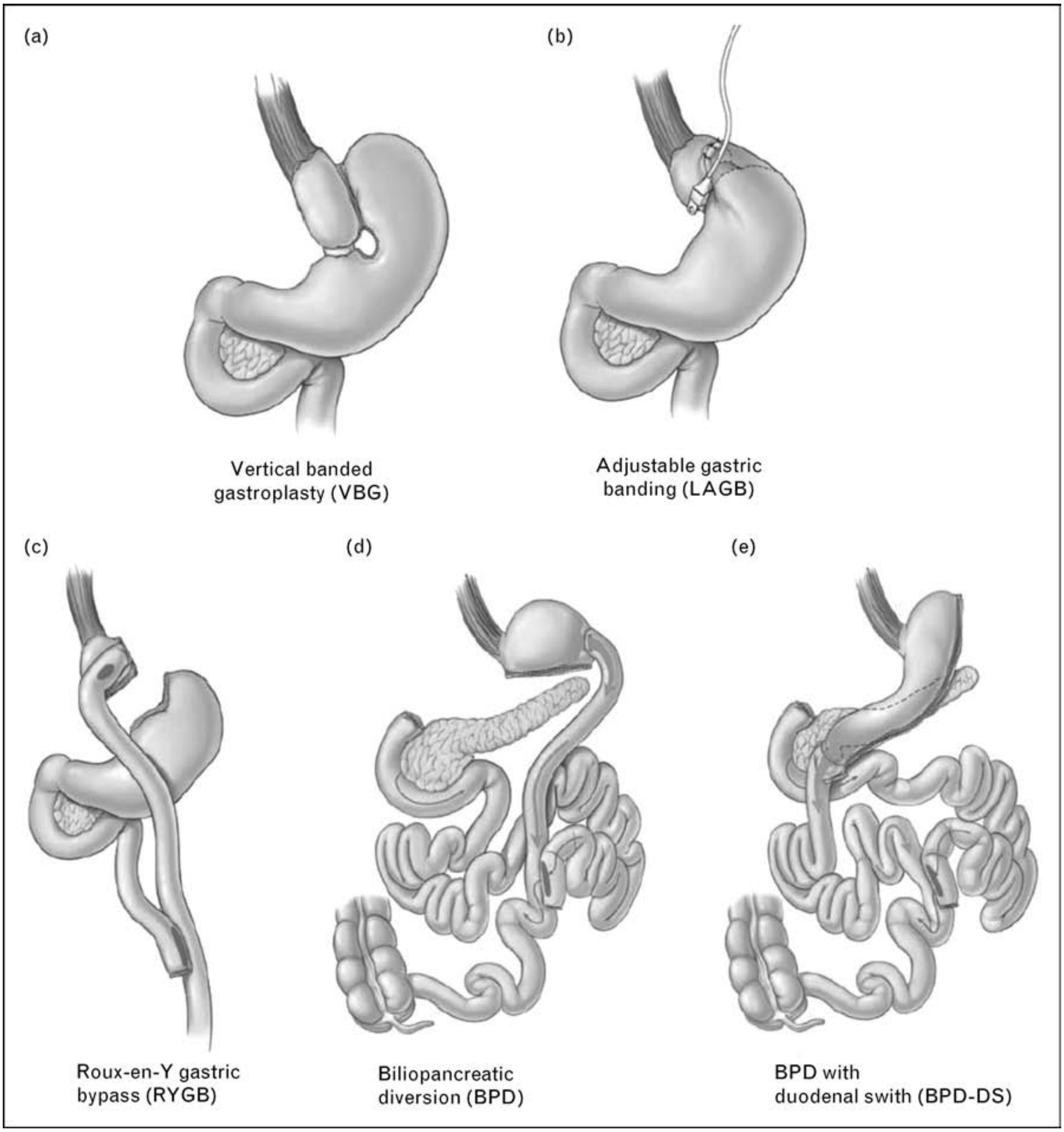
> - Bariatric surgery is the only effective treatment for severe obesity that not only provides long-term and sustained weight loss but resolution of nearly all obesity associated comorbid conditions, improving overall survival and decreasing cancer rates.
> - Bariatric surgery provides resolution of T2DM in more than 80% of obese patients.
> - The understanding of the mechanistic pathways for T2DM resolution after bariatric surgery may help in the identification of suitable therapeutic targets for the treatment of T2DM.

Novel bariatric surgery

The duodenojejunal bypass (DJB) has gained interest in the last few years. It is a stomach-sparing bypass of a short portion of proximal intestine. DJB has improved glucose homeostasis in rat models of T2DM independent of food intake, weight or absorption [20,21]. Lean T2DM patients who underwent DJB also achieved glycemic control as early as 1 month after surgery [22]. Importantly, these glycemic changes were also weight independent. The DJB when combined with a sleeve gastrectomy resection has proven to be of benefit for severely obese patients with T2DM [23]. The weight loss for this combined DJB–sleeve gastrectomy procedure was similar to that achieved with the RYGB. However, recent reports in T2DM rat models have doubted the role of the proximal intestinal hypothesis [24,25]. The ileal transposition in combination with sleeve gastrectomy is yet another novel bariatric procedure under investigation (SGIT) [26]. The SGIT interposes a segment of ileum into a proximal jejunal loop that enhances an incretin response. This procedure, when performed in lean T2DM patients, achieved similar glycemic responses when compared to standard restrictive and malabsorptive procedures [27–29]. The endoluminal duodenojejunal sleeve (ELS), which is a plastic sleeve device, is placed endoscopically in the prepyloric area and deployed distally bypassing the duodenum. Experimental results in rats have shown marked improvements in glucose homeostasis that are independent of nutrient malabsorption [30]. Initial ELS human trials showed equivalent glycemic results [31]. Furthermore, when the ELS device was used in obese patients, substantial weight loss was observed at 12 weeks [32]. The standard and novel bariatric procedures presented show promising effects on glucose homeostasis and which may elucidate the pathophysiology and proposed mechanisms of T2DM resolution.

Figure 1 Types of bariatric surgery



Adapted with permission from [6].

Bariatric surgery in type 2 diabetes mellitus and BMI less than 35 kg/m^2

Mildly obese patients with a BMI between 30 to 35 kg/m^2 and T2DM are still at risk from obesity-related comorbid conditions, but yet bariatric surgery is not available to them. The standard bariatric procedures as described above have been performed in this mildly obese subgroup. In a randomized trial comparing AGB vs. medical therapy for patients with BMI 30–40 kg/m^2 and T2DM, remission was achieved in 73% of those who underwent AGB compared with 13% in the medical group with increased weight loss in the surgical group at 2 years [33]. Similar improvements in glucose homeostasis have been found in mildly obese patients after RYGB and BPD–duodenal switch [34,35]. Most recently, the FDA evaluated and approved the AGB as an indication for patients with T2DM and a BMI less than 35 kg/m^2. Penalizing the patients because they lose weight before surgery below the BMI threshold or asking them to gain weight to become surgical candidates is unreasonable. This is still an area of controversy and of intense research.

Bariatric surgery effects on type 2 diabetes mellitus

Data from recent prospective and retrospective cohort studies have shown that weight loss induced by bariatric surgery can achieve remission of type 2 diabetes mellitus

(T2DM) [11,36,37]. The results of these meta-analyses demonstrated that T2DM resolves in approximately 80% of patients who have had RYGB and BPD–duodenal switch surgeries. Conversely, the resolution rates are slightly lower with restrictive-only procedures but greater than any available medical therapy. In addition, it has been theorized that bariatric procedures that divert ingested nutrients away from the upper gastrointestinal tract have vital effects on glucose homeostasis [6,20,38]. Moreover, bypassing the upper gastrointestinal tract also leads to improvement in glycemic control in T2DM within a few days after surgery, before significant weight loss occurs that is also independent of restrictive caloric intake. These data suggest that mechanisms other than weight loss alone account for the beneficial effect of bariatric surgery on T2DM, likely by an incretin effect. This observation has led to the notion that bypassing the upper gastrointestinal tract has specific therapeutic effects on insulin action and glucose metabolism. The beneficial effects on glucose homeostasis after bariatric surgery are likely due, in large part, to the effect of weight loss on insulin sensitivity and possibly additional beneficial effects on β-cell function and the metabolic response to feeding. Furthermore, it has been observed that those obese patients with shorter duration of T2DM (less than 5 years), mild forms of T2DM (no insulin requirements) and having the greatest weight loss are more likely to have a remission of T2DM when compared with those with longer duration of the disease or chronic T2DM (more than 10 years), and are on insulin therapy [10,37]. This hypothesis has led to the concept that the duration and severity of T2DM is inversely correlated to the likelihood of remission that may be explained in part by chronic and acquired β-cell dysfunction (*i.e. obesity related pancreas burnout*). Therefore, it is possible that early surgical intervention, as early as the adolescence, may be necessary for T2DM and obese patients to increase the likelihood of rendering them euglycemic, therefore preventing permanent and irreversible pancreatic lipotoxicity and β-cell damage. This hypothesis has not been adequately tested in humans yet. Bariatric surgery in the adolescent population is still controversial; however, the short-term outcomes are encouraging [17].

Bariatric surgery effects on insulin sensitivity and beta-cell function

It has been demonstrated that RYGB provides a more rapid improvement effect in glucose regulation, insulin sensitivity and beta-cell responsiveness to glucose when compared with bariatric procedures that lack gastrointestinal bypass [39••]. Specifically, during a two-stage hyperinsulinemic euglycemic clamp, the hepatic, skeletal muscle and adipose tissue insulin sensitivity in non-T2DM patients improves significantly after weight loss at 1 year after RYGB when compared with baseline values [40••]. In addition, these glucose metabolism improvements occur as early as 1 month [41]. Similar studies have shown normalization in insulin sensitivity and β-cell function in diabetic and nondiabetic patients after RYGB at 2 years [42]. Furthermore, a dual mechanism for these glucose responses have been postulated [43••]. In patients exhibiting hyperglycemia before surgery, glucose control improved early following RYGB because of increases in insulin secretion (β-cell function), whereas long-term improvements of glucose control are due largely to reduced adiposity (i.e. lipotoxicity resolution) and weight loss. This hypothesis may explain in part what has been observed clinically for years after proximal gastrointestinal bypass operations. Nevertheless, restrictive-only procedures that lack gastrointestinal bypass have also shown improvements in insulin sensitivity that appear to be weight loss related [33,44,45]. Most recently, it was shown by hyperinsulinemic and euglycemic clamps that improvements in peripheral glucose uptake following RYGB were observed only after substantial weight loss had occurred and correlated with the magnitude of weight lost [46••].

Nonbariatric surgery effects on insulin sensitivity

Other nonbariatric procedures that aim at visceral or peripheral adipose reduction such as omentectomy (surgical removal of the greater omentum) and abdominal liposuction, respectively, have been previously studied. It was hypothesized that these adipose compartments had a role on insulin resistance. Obese T2DM patients who underwent omentectomy with or without RYGB did not show any improvement in metabolic function by means of hyperinsulinemic and euglycemic clamps [47••]. Similarly, abdominal liposuction did not significantly alter the insulin sensitivity of muscle, liver, or adipose tissue and did not significantly affect other risk factors for coronary heart disease [48]. The visceral and peripheral adipose compartments and their contribution to insulin resistance have been, therefore, put to rest.

Proposed mechanisms of type 2 diabetes mellitus resolution

It is well known that even modest reduction in weight because of caloric restriction results in glucose homeostatic improvement [49]. But certainly, surgery-induced weight loss and subsequent decreases in adiposity and lipotoxicity are responsible for the long-term benefits in metabolic function [50]. There is now evidence that bariatric surgery that involves a proximal gastrointestinal bypass exerts an almost immediate and long-standing impact on glucose homeostasis, β-cell function and insulin sensitivity. In addition, these improvements have been found to be weight loss independent. Furthermore, those bariatric procedures involving gastrointestinal bypass offer higher and faster rates of T2DM resolution compared with those that are restrictive only. Finally, a rare hyperinsulinemic–hypoglycemic syndrome has been described after RYGB [51]. This is likely the result of the insulinotropic effects offered by the RYGB procedure including β-cell hypertrophy and resulting hyperinsulinemia. It was recently demonstrated that these effects are not related to overexpression of glucagon-like peptide-1 receptors when compared with insulinoma specimens [52]. Most recently, animal models have been created to study this β-cell hypertrophy and incretin effects [53]. Early nutrient small bowel stimulation which is a common feature for bypass procedures and nonbypass such as the sleeve gastrectomy, because of rapid sleeve emptying, has been suggested to be involved in the incretin responses after surgery (foregut hypothesis) [20]. Additionally, it appears that the early stimulation of the distal small bowel may also have an important incretin effect as demonstrated by the SGIT procedure (hindgut hypothesis) [26].

Conclusion

Bariatric surgery induced weight loss, including novel bariatric surgical procedures, offers a unique opportunity to understand the pathophysiology of T2DM and to identify the potential pharmacologic targets for the cure of T2DM.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 417).

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