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Do Incretins Play a Role in the Remission of Type 2 Diabetes after Gastric Bypass Surgery: What are the Evidence?

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Abstract

Gastric bypass surgery (GBP), in addition to weight loss, results in dramatic remission of type 2 diabetes (T2DM). The mechanisms by which this remission occurs are unclear. Besides weight loss and caloric restriction, the changes in gut hormones that occur after GBP are increasingly gaining recognition as key players in glucose control. Incretins are gut peptides that stimulate insulin secretion postprandially; the levels of these hormones, particularly glucagon-like peptide-1, increase after GBP in response to nutrient stimulation. Whether these changes are causal to changes in glucose homeostasis remain to be determined. The purpose of this review is to assess the evidence on incretin changes and T2DM remission after GBP, and the possible mechanisms by which these changes occur. Our goals are to provide a thorough update on this field of research so that recommendations for future research and criteria for bariatric surgery can be evaluated.

Keywords

Incretin; GLP-1; GIP; Diabetes; Gastric bypass; Insulin; Weight loss

Introduction

The prevalence of type 2 diabetes (T2DM) has increased rapidly over the last several decades, both in the US and many developing countries. Obesity is a strong risk factor for T2DM, lending to the term “diabesity,” or obesity with accompanying T2DM. In the last several years, bariatric

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surgery has become an increasingly preferred option for weight loss and treatment of obesity-related metabolic complications in morbidly obese individuals. In 2007, 170,000 bariatric surgery operations were performed in the US, a >9-fold increase from 1999 [1,2]. In the emergence of the diabesity epidemic, bariatric surgery not only results in significant and sustained weight loss but in many patients also puts T2DM in remission. Compared to conventional diet and pharmacological weight loss treatments, which induce a modest 10% weight loss of short duration and are often followed by weight regain [3], bariatric surgery results in 50% excess weight loss with control of T2DM in 76% of patients [4,5]. Using bariatric surgery as a treatment for T2DM independently of morbid obesity, as suggested by clinical studies [6,7], and recently publicized by the lay press [8], is an emerging concept; however, there is a need for more well-designed trials to clearly determine how bariatric surgery elicits these effects and, more importantly, the clinical applicability of these procedures as a treatment option for T2DM. The goal of this review is to evaluate the currently proposed mechanisms by which T2DM is controlled after gastric bypass surgery (GBP), principally in relation to the role of the incretins, based on the available evidence from clinical trials and experimental data from human and animal studies. Several reviews have addressed changes in gut hormones after bariatric surgery in relation to T2DM [9-12]; nevertheless, updates such as these may provide clinicians, researchers, and the public a comprehensive understanding of the current status of the bariatric surgery field. These assessments may eventually help develop less invasive or safer alternatives to surgery.

Background

Pathophysiology of T2DM: Role of Incretins

T2DM is characterized by defects in multiple organs, including decreased glucose uptake into skeletal muscle, pancreatic deficiency (illustrated by defects in β-cell function with impaired insulin secretion and defects in α-cell function with increased glucagon secretion), increased liver glucose output, and the reduced effect of incretins, gut hormones that stimulate insulin secretion after a meal [13,14].

The two major gut hormones that have been identified as incretins are gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP is secreted from the K cells located mainly in the duodenum, while GLP-1 is secreted from the L cells found mainly in the ileum [15, 16]. The incretins are rapidly secreted during a meal, circulate in the blood, and have a relatively short half-life (3–7 min), as they are rapidly inactivated by the enzyme dipeptidyl peptidase-IV (DPP-IV) [17,18]. Incretin hormones increase insulin secretion in response to glucose [19,20]. The incretin effect on insulin secretion was originally described by Creuzfeldt and Ebert [21] as the greater insulin response from an oral glucose load compared to that after an equivalent rise in blood glucose from an intravenous glucose load.

The effects of incretins on glucose homeostasis have been well reviewed [15,22,23]. The main function of incretins is to stimulate glucose-dependent insulin secretion. Both in vivo and in vitro studies showed that GLP-1 in pancreatic β-cells stimulates insulin biosynthesis [24,25]. In addition to its insulinotropic effects, GLP-1 exerts its glucose-lowering effects through inhibition of gastric emptying [26-29], restoration of insulin sensitivity [26], and inhibition of glucagon secretion [29,30], which may result in the decrease of hepatic glucose production [31,32]. GLP-1 agonists also have been shown to increase β-cell mass and pancreas islet size in rodents [20,33]. GLP-1 receptors have been identified on β-cells of both rats and humans [34,35], and studies have demonstrated that disruption of the GLP-1 receptor results in enhanced apoptosis of β-cells [36].

In patients with T2DM, the incretin effect is diminished [37]. Plasma measurements (fasting and postprandial) of GIP are normal compared to patients without T2DM, but administration

of exogenous GIP does not increase insulin secretion [38], suggesting GIP resistance in T2DM, although the GIP response is restored if glycemia is normalized [39]. GLP-1 levels are generally [40] but not always [41] found to be lower in T2DM. In contrast to GIP administration, patients with T2DM respond to exogenous GLP-1 [42].

Clinical Use of Incretins in T2DM

Most patients with T2DM require a combination of oral antidiabetic agents, followed eventually by insulin treatment. Weight gain and fear of hypoglycemia are often barriers to treatment compliance and glycemic control. Incretin mimetics that are resistant to the effect of DPP-IV as well as DPP-IV inhibitors have recently been developed and are currently in use as treatment for T2DM (as reviewed in [43]). Similar to conventional oral hypoglycemic agents and insulin therapy, incretin mimetics and DPP-IV inhibitors significantly lower hemoglobin A1C (HbA1C) and postprandial glucose excursions in patients with T2DM and often without the added weight gain. Nevertheless, the durability of these effects and their potential long-term benefits are still largely unknown.

Bariatric Surgeries

There are three main categories of bariatric surgery: restrictive, malabsorptive, and a combination of the two. Restrictive bariatric surgeries are based on a reduction of the stomach size to increase satiety and subsequently reduce food intake. Vertical banded gastroplasty (VBG) staples the stomach vertically using a synthetic material sutured around the stomach [44]. Laparoscopic adjustable gastric banding (GB), currently the most common restrictive bariatric procedure, consists of a constricting silicone band that is 10–12 mm in diameter, inserted laparoscopically. This band contains a volume-adjustable compartment on its inner surface connected to a subcutaneous port device. The size of the band is controlled by saline infusion to this port [9,45]. The size of the proximal gastric pouch is about 20–30 ml (Fig. 1a). GB results in about 40.7–54.2% excess weight loss [4].

Malabsorptive surgeries are based on the principle of bypassing certain portions of the intestine so that food is not absorbed. Strictly, malabsorptive procedures include jejunoileal bypass (JIB) and biliopancreatic diversion (BPD); however, these surgeries currently are not frequently performed due to several undesirable side effects, such as severe macronutrient and vitamin deficiencies. The most commonly performed bariatric procedure in the US is Rouxen-Y GBP [1], which is a combination malabsorptive–restrictive surgery. GBP surgery entails division of the stomach into a small proximal pouch that holds about 20–30 ml and a larger distal portion that is bypassed. The small pouch is then anastomosed to the distal part of the ileum (alimentary limb). The remaining larger portion of the stomach, the duodenum, and the jejunum are reattached to the distal part of the ileum (below the gastroileal anastomosis) to allow for excretion of gastrointestinal and pancreatic juices (biliopancreatic limb; Fig. 1b) [9,45,46]. GBP results in about 56.7–66.5% excess weight loss [4].

Effect of Weight Loss on T2DM Control

Diet-Induced Weight Loss—T2DM is often associated with overweight and/or obesity and two thirds of patients with T2DM have a body mass index (BMI) of 27 kg/m^2 or greater [47]. Although patients with T2DM often require a combination of medications, oral and insulin; the cornerstone of treatment is weight loss. There are many short-term studies showing improvement of T2DM control by diet or diet and exercise, with or without pharmacological treatment [48-52]. Both caloric restriction and the weight loss itself account for the major ameliorating effects of dietary intervention on T2DM [53,54]. However, diet-induced weight loss is often of short duration and is usually followed by weight regain [3].

Surgical Weight Loss: Clinical Outcome in T2DM—In contrast, bariatric surgery results in weight loss of great magnitude (up to 33% weight reduction) sustained over time [55]. In addition to its substantial weight loss effect, bariatric surgery has been shown to result in T2DM remission. A meta-analysis in 2004 reported that GBP resulted in remission of T2DM in 83.7% of its cases, while GB produced T2DM remission in 47.9% of patients [4]. Many studies report decreases in fasting glucose, insulin, hemoglobin A1c (HbA1c), markers of insulin resistance, and medication usage as a result of surgery (Table 1). Although the spectacular effect of malabsorptive procedures such as GBP or BPD on T2DM remission is well known, some studies have also reported positive results on the effects of GB on remission of T2DM [56,57]. A recent randomized clinical trial showed dramatic effects of GB, reporting 73% T2DM remission (defined as HbA1c levels <6.2%, fasting glucose <126 mg/dl, and cessation of T2DM medication usage) at 2 years [5]. These remarkable results on T2DM remission after surgical weight loss may have a broad clinical impact, on both the quality of life for patients, who often are required to take multiple medications for T2DM and related conditions, and also on the cost of health care.

Potential Mechanisms for T2DM Remission after GBP

Changes in Incretins

Many studies have examined changes in gastrointestinal hormones, including incretins, after surgery, in relation to both glucose homeostasis and satiety effects. The major longitudinal studies that have studied incretin levels after bariatric surgery are summarized in Table 2. Early studies showed increased fasting and postprandial enteroglucagon (a previously used marker for GLP-1) levels after both GBP and JIB [58,59]. In 1998, a cross-sectional study by Naslund et al. [60] reported dramatic increases in GIP and GLP-1 levels in JIB patients 20 years postoperatively compared to nonoperated obese and lean control patients.

GLP-1—The changes in GLP-1 levels after bariatric surgery have been extensively studied in the last 10 years. Several studies showed either no change [61-64] or an increase [65,66] in fasting GLP-1 levels after malabsorptive surgeries, although one longitudinal study recently reported a decrease in fasting GLP-1 levels in obese patients 2 years after GBP [67].

The postprandial GLP-1 response after bariatric surgery, in contrast, has been more consistent, with all studies reporting unanimously an increase of GLP-1 levels during an oral glucose tolerance test (OGTT) or mixed test meal after GBP or BPD in obese subjects [65,68-70], as well as in patients with T2DM after BPD [66] or GBP [62,64]. The GLP-1 increase occurs as early as 2 days after GBP [71] and persists at 6 months and 1 year [72]. Purely restrictive procedures do not result in an increase of GLP-1 [65,73-75].

GIP—Fewer studies have reported the effects of bariatric surgery on GIP levels. Additionally, the results have not been as consistent as those reported for GLP-1. Many studies have observed a reduction [66,76] or no change [62,64] in fasting GIP levels after BPD or GBP. No studies to date have reported and increase in fasting GIP after surgery. Stimulated GIP levels decreased after a test meal in obese patients 2 weeks after JIB [77] or after GBP and BPD [66,76]. In our own study in patients with T2DM, GIP levels increased during an OGTT 1 month after GBP [62,64], an effect that did not persist over time [72]. This is in agreement with several cross-sectional studies reporting increased postprandial GIP levels after GBP or JIB [60,77,78], 6 months to 20 years after surgery. Overall, the variability in GIP levels in these studies may be due to the time after surgery, T2DM status and the overall metabolic control of these patients. Nevertheless, despite this variability, the literature suggests that these effects are distinct from those of purely restrictive surgeries, as studies have reported no effect on GIP after VBG or GB [65,73,75].

In addition to the increase of meal- or glucose-stimulated GLP-1 and GIP levels occurring after bypass procedures, we have shown that the incretin effect on insulin secretion, impaired in patients with T2DM, returns to the level of controls 1 month after the surgery [64]. The normalization of the incretin effect, in patients with recently diagnosed T2DM (less than 5 years) persists at 1 year after surgery [72].

Other Changes in Glucose Homeostasis after Bariatric Surgery: Hepatic Glucose Production

There are very few studies that have reported the effect of bariatric surgery on hepatic glucose production (HGP). One recent cross-sectional study observed earlier suppression of HGP during an oral glucose load (as measured by glucose appearance using isotope-labeled glucose tracers) in GBP patients 1–4 years after surgery [74]. Another prospective study using similar methods reported decreased endogenous glucose production 1 year after GBP [79].

Patients with T2DM have hyperglucagonemia which improves with diet-induced weight loss [80,81]. Additionally, glucagon levels are suppressed after administration with a GLP-1 analog [82]. With weight loss and the increase of GLP-1 observed after GBP, a decrease of glucagon levels following GBP surgery is expected. This has been shown in one cross-sectional study, where GBP patients exhibited decreased glucagon levels 180 min after a test meal compared to nonoperated BMI-matched control subjects [73]. In contrast, we [62] and others [78] have observed an increase of glucagon levels after GBP. The reasons for this are unclear.

Other Changes in Glucose Homeostasis after Bariatric Surgery: Insulin Resistance and Secretion

One major characteristic of T2DM is insulin resistance, normally manifesting in a reduced insulin-mediated glucose uptake. Many studies have shown a decrease of insulin resistance after bariatric surgery, determined either by homeostasis model assessment for insulin resistance (HOMA-IR) [83,84], quantitative insulin sensitivity check index [85], intravenous glucose tolerance test (IVGTT) [68,86], or by the gold standard measurement of insulin sensitivity, the euglycemic–hyperinsulinemic clamp [66,87,88]. This effect seems to occur rapidly after surgery and often prior to substantial weight loss [85-87]. In longer studies, however, insulin sensitivity appears to be related to the degree of weight loss [57,89]. Recent comparisons of GBP and GB have shown no significant difference on insulin resistance between the two interventions [83,84], suggesting that caloric restriction and weight loss following surgery, rather than the nature of the procedure, is a major factor in the improvement of insulin sensitivity after bariatric surgery. However, GLP-1 [26,29] may improve insulin sensitivity, but its role and that of other gut peptides such as peptide YY (PYY) [90,91] and ghrelin [92] in increasing insulin sensitivity, above and beyond caloric restriction and weight loss, require further study.

T2DM is also characterized by a defect in early-phase insulin secretion after oral stimulus and/or first-phase insulin secretion during IV glucose challenge [93]. The biphasic insulin response to a rapid IV glucose challenge is abnormal in T2DM; the first-phase insulin secretion, seen over the first 10 min, is absent [94].

Commonly used tools to assess insulin secretion in patients include IVGTT and insulin response to glucose. Weight loss by dietary restriction improves insulin secretion, possibly by decreasing glucose and free fatty acid toxicity to the β-cell [50,95]. Surgical weight loss has been shown to restore first-phase insulin secretion in obese subjects with T2DM [85,96] as measured by IVGTT. This is also demonstrated in patients with impaired glucose tolerance, as shown by frequently sampled intravenous glucose tolerance test (FSIVGTT) [97] or insulin response to arginine [98]. Infusion of the GLP-1 or a GLP-1 analog increased first-phase insulin secretion in patients with T2DM [99] and in normoglycemic subjects [100]; the increase of

postprandial incretins after malabsorptive surgeries may participate in the improvement of insulin secretion, although this has not been extensively studied. Nevertheless, the insulin secretory capacity of patients with T2DM is highly variable [101,102]. Accordingly, the effects of weight loss on insulin secretion will be mainly dependent upon the β-cell capacity and the degree of hyperglycemia [103].

Mechanisms of Increased Incretins After GBP

There are several proposed mechanisms for the increase in incretin levels after GBP, although to date none have been clearly established, and the results of many studies often conflict with one another.

Weight Loss

In 2001, Verdich et al. [104] reported a 9.2% increase in meal-stimulated GLP-1 area under the curve (AUC) over 3 h after a 6-month dietary weight loss program (~20-kg weight loss) in a group of obese nondiabetic patients. However, we recently showed that GLP-1 levels during an OGTT did not change significantly after a 10-kg diet-induced weight loss in obese subjects with T2DM [62]. The reasons for these discrepancies could be attributable to the difference in weight loss amount and/or T2DM status. Additionally, we found that an equivalent weight loss 1 month after GBP increased GLP-1 AUC during a 3-h OGTT by >300% [62]. These data suggest that it is unlikely that weight loss contributes to increased incretin levels; the surgical nature of GBP appears to play a much greater role in this increase than weight loss per se.

Gut Exposure to Nutrients

Rapid Hindgut Delivery Hypothesis—One proposed hypothesis regarding the mechanisms of increased incretins following GBP is the rapid exposure of the lower small intestine to nutrients. Several groups have examined this hypothesis. In 2005, Strader et al. [105] reported the effects of ileal interposition (IT) in high-fat-fed obese nondiabetic Long-Evans rats. This procedure, where a segment of the ileum is relocated to the proximal small intestine, was able to specifically assess the effect of rapid ileal exposure without any other gastric restriction or intestinal rerouting. IT increased plasma GLP-1 levels during an OGTT 3 weeks after surgery compared to sham-operated rats. However, the surgery did not affect glucose or insulin levels, which were difficult to assess in these nondiabetic rats with essentially normal glucose levels. A study in a model of nonobese diabetic Goto-Kakizaki (GK) rats showed that glucose tolerance improved during an OGTT 30 days after IT [106]. Plasma GLP-1 levels during the first 15 min of the OGTT, measured 45 days after IT, were significantly increased compared to sham-operated controls. The same group later demonstrated an improvement in glucose tolerance with a decreased glucose AUC during an OGTT in GK rats 45 days after IT compared to sham-operated or nonoperated rats [107]. The authors also reported increased insulin levels during the OGTT with increased insulin sensitivity 5 months after IT compared to control groups. There was no effect of IT on glucose-stimulated GLP-1 levels (as measured by GLP-1 AUC) by 6 months postsurgery, although IT rats exhibited a prolonged GLP-1 response during the OGTT and increased proglucagon mRNA expression in the ileum compared to those of the sham-operated or nonoperated controls.

Recently, one group examined the clinical effects of IT in remission of T2DM [6]. In this study, IT to the proximal jejunum followed by a sleeve gastrectomy was performed on 39 T2DM patients with a presurgery BMI of 30.1 kg/m^2. Seven months after surgery, patients lost an average of 22% of their presurgery body weight (postsurgery BMI 24.9 kg/m^2) and showed significantly decreased HbA1c (by 28%), fasting (by 44.6%) and postprandial glucose (by 45.3%) levels, and HOMA-IR (by 50%). Incretin levels were not reported in this study.

Foregut Exclusion Hypothesis—A second proposed hypothesis regarding the mechanisms of increased incretin levels after GBP is the exclusion of the foregut from nutrient exposure. This concept was first proposed when Hickey et al. [108] observed in a cross-sectional study that glucose tolerance and insulin sensitivity in a group of patients who had undergone GBP were significantly improved compared to a group of weight-matched (postsurgery) controls. In 2004, Rubino and Marescaux [109] reported the effects of a gastrojejunal bypass (GJB) procedure on glucose homeostasis in diabetic GK rats. Fasting glucose was significantly decreased over the 32-week period following GJB, and glucose tolerance was improved (AUC during a 3-h OGTT) 1 week after GJB compared to sham-operated controls. Insulin sensitivity was also improved (as measured by glucose disappearance during an insulin tolerance test) 20 weeks after surgery in GJB rats compared to controls. In addition, there was an increase in fasting GIP levels in GJB rats 2 weeks postsurgery compared to preoperative levels [109]. These observations were made in the absence of any significant difference in body-weight change or food intake between the GJB and the sham-operated controls.

In an effort to distinguish foregut exclusion from rapid hindgut exposure in the T2DM-related effects after GBP, Rubino et al. [110] designed a study where GK rats received either a duodenal-jejunal bypass surgery (DJB) or a gastrojejunostomy (GJ) to allow for rapid ileal exposure to nutrients without foregut bypass. DJB rats showed improved oral glucose tolerance (as measured by decreased glucose AUC during an OGTT) compared to both GJ and sham-operated control rats 10 days after surgery. In addition, a subsequent reoperation where the GJ was converted to a DJB significantly improved glucose tolerance compared to before the conversion procedure. In contrast to the effects observed in GK diabetic rats, DJB performed on normoglycemic Wistar rats resulted in a significant decrease in glucose tolerance compared to sham-operated control Wistar rats. The authors concluded that there may be a factor present in the proximal intestine that contributes to the T2DM phenotype, and bypass of this portion of the small intestine may ameliorate T2DM. However, this procedure may disrupt glucose homeostasis in nondiabetic conditions. Incretin levels, incidentally, were not reported in this study. A recent study compared the effects of IT and DJB on glucose, insulin, and GLP-1 levels in GK rats [111]. This study reported similar effects between DJB and IT on improved tolerance (as measured by glucose AUC during an OGTT) 4 weeks postsurgery. Mean GLP-1 levels 30 min after an oral glucose load were lower in the DJB group compared to the IT group by 1 week after surgery, but both surgery groups exhibited higher GLP-1 levels compared to sham-operated controls by 4 weeks after surgery. These results suggest that both foregut exclusion *and* rapid hindgut exposure equally improve glucose tolerance; both principles may be key players in T2DM remission after GBP. However, these effects on glucose tolerance may be mediated through different mechanisms. Rapid hindgut exposure to nutrients may be related to increased GLP-1 levels after surgery, while duodenal exclusion may mediate some of its effects independent of changes in GLP-1.

Still, others report no effect of foregut exclusion or rapid ileal exposure to nutrients during GBP on changes in incretin levels, despite the improvement in glucose tolerance. A study by Pacheco et al. [112] also found that duodenal-jejunal exclusion in GK rats, similar to the procedure described in Rubino et al. [61], decreased fasting glucose and glucose levels during an OGTT by 1 week after surgery compared to nonoperated control GK rats. There was no effect of the procedure on glucose-stimulated GLP-1 or GIP levels compared to controls; however, there was a significant decrease in glucagon and leptin levels following the glucose load 1 week after surgery. The authors suggested that the rapid improvement of glucose homeostasis observed by duodenal-jejunal bypass might be mediated by the decrease in leptin levels, which may stimulate insulin secretion, although no changes in glucose-stimulated insulin levels after surgery was observed.

Gut motility–Gastric Emptying—The gastrointestinal tract is increasingly regarded as an important organ in glucose homeostasis, and both gut motility and gastric emptying may play an important role in postprandial glucose control [13]. Few groups, however, have reported the effect of GBP on gut motility and gastric emptying, and results have varied among studies. Horowitz et al. [113] reported in a 1986 cross-sectional study that gastric emptying of solids was slower in GBP patients compared to nonoperated control patients; however, gastric emptying of liquids was faster in GBP patients. Naslund and Beckman [114] later reported in a longitudinal study reduced pouch emptying at 2 months after GBP. Similarly, a small number of studies are available on gut motility after bariatric surgery. Kotler et al. [115] showed increased intestinal transit time and increased enteroglucagon levels after various types of gastric surgery in weight-losing subjects compared to postsurgery weight-stable subjects. A recent study demonstrated accelerated gastric emptying and shortened intestinal transit time in morbidly obese subjects 6 weeks after GBP. This was accompanied by an increased postprandial GLP-1 response, which was significantly correlated with the gastric-emptying response after surgery [69].

Other Proposed Mechanisms of T2DM Resolution After GBP (Ghrelin, Peptide YY, Leptin)

In addition to incretins, there are also a number of other hormones that are altered after GBP which may be integral in the maintenance of glucose homeostasis.

Ghrelin is a hormone produced by the stomach and may play a role in short- and long-term energy balance. Administration of ghrelin or its analogs stimulates food intake [116,117], and ghrelin levels vary as a function of BMI and weight change. Obese individuals have lower circulating ghrelin levels. Weight loss by diet increases ghrelin levels, increasing food intake [118,119]. In contrast, ghrelin levels do not rise after GBP in spite of considerable weight loss [118,120-123], which may influence caloric intake and subsequently glucose homeostasis. Additionally, recent studies have proposed other roles for ghrelin related to T2DM. Ghrelin has been shown to inhibit insulin secretion in humans [124,125], and a recent study demonstrated that genetic knockout of ghrelin in lean mice reduced fasting glucose levels and endogenous glucose production and increased glucose-stimulated insulin levels compared to wild-type mice [92]. In diabetic *ob*/*ob* mice, ghrelin deletion reduced fasting glucose and fasting insulin and improved glucose tolerance [92].

PYY is cosecreted with GLP-1 from intestinal L cells in response to food intake. PYY_{3-36} has been shown to decrease food intake in humans [126] and regulates body weight in rodents [127]. Cross-sectional [74,128] and longitudinal [69,129] studies have reported increased PYY levels after GBP, which may partially explain the reduced caloric intake and improved glucose homeostasis after surgery. A study in our laboratory recently found increased PYY_{3-36} levels 1 month after GBP; this effect was not observed after a matched weight loss achieved with dietary restriction (Oliván et al. in review). Similar to ghrelin, there are recent studies that have suggested more direct effects of PYY on insulin sensitivity [90]; however, the role of PYY independent of food intake still needs to be confirmed.

Leptin, which is secreted from the adipose tissue, is also involved with food intake and long-term energy regulation [130,131]. However, in contrast to ghrelin, leptin levels are generally higher in obese individuals. Several studies showed a reduction of leptin levels after GBP [123,128,132], some of which indicated this reduction was correlative with weight or BMI [128,132]. Some studies, however, have shown reduction in leptin levels which were not correlated with weight and fat mass loss [108,133], suggesting an increase in leptin sensitivity after GBP; this may play a role in glucose homeostasis. A recent study in GK rats showed

decreased leptin levels 1 week after duodenal exclusion surgery compared to nonoperated GK rats [112].

These hormones may act in concert with the incretins, or one hormone may potentiate the action of another, although the currently available data implicating these hormones in T2DM remission after surgery are minimal and controversial. There is a need for more carefully designed clinical trials, beyond descriptive studies, that will confirm these hormonal changes and determine whether or not they play a role in T2DM-related changes after GBP.

Conclusions

It is well-documented that T2DM remission occurs after bariatric surgery. First and foremost, the effect of caloric restriction and subsequent weight loss clearly plays an important role in this remission. This is evident by the restoration of glucose tolerance, decreased HbA1c levels, and improvement of insulin sensitivity by all categories of bariatric surgery. Alterations in the small intestinal anatomy after GBP may also be integral in T2DM control. Foregut exclusion or rapid delivery of food to the hindgut may be responsible for increased incretin levels, which can promote insulin secretion and also possibly increase insulin sensitivity. GLP-1 appears to be consistently increased after GBP, and these changes are often related to improvement of glucose homeostasis. The role of GIP and how it changes after GBP are less clear and require further research. There also may be changes in ghrelin, PYY, and gastric emptying that occur as a result gastrointestinal tract rerouting after GBP, although these findings in relation to T2DM remission necessitate more investigation. Figure 2 shows a schematic of the potential mechanisms by which T2DM is resolved after bariatric surgery, based on the existing literature.

Future Directions

Despite the research available, there are significant limitations in the previous studies. A large number of the studies that have examined hormonal changes in relation to glucose homeostasis after surgery have been conducted in nondiabetic subjects. The role of T2DM status and duration needs to be addressed in terms of the effectiveness of bariatric surgery. Long-term studies are needed to test not only the impact of T2DM remission on cardiovascular outcome but also the metabolic consequences of elevated incretin levels on hypoglycemia after GBP surgery.

Mechanistic studies to elucidate the role of caloric restriction versus weight loss, the role of the vagus nerve on gut peptide release, and the duodenal exclusion versus ileal exposure to nutrients are necessary. The mechanisms by which appetite is reduced after GBP or with GB will also need to be studied, as decreased calorie intake is a major component of weight loss. Finally, although most patients benefit from bariatric surgery with sustained weight loss, some patients regain the weight lost initially after surgery [134]. Understanding the predictors and the mechanisms of failure after bariatric surgery will be an important factor in better patient selection for bariatric surgery.

The current recommendations for bariatric surgery in the US are BMI$\geq$35 kg/m^2 with comorbidities or BMI$\geq$40 kg/m^2 without comorbidities. In view of the multiple benefits of the surgery and the recent report of increased longevity after bariatric surgery [135], these criteria may need to be revised and surgery be offered at lower BMI. Nevertheless, it is premature to advocate experimental bariatric procedures to nonobese patients with T2DM. Recent developments in experimental bariatric surgery such as ileal interposition [6], endoluminal [136], and minigastric bypass surgery [7] will require more careful research trials before becoming clinically applicable on a larger scale. It is imperative to clearly understand how these treatments are improving metabolic conditions such as T2DM.

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Abbreviations

T2DM	type 2 diabetes mellitusy
GBP	gastric bypass surgery
GIP	gastric inhibitory peptide-1
GLP-1	glucagon-like peptide-1
DPP-IV	dipeptidyl peptidase-IV
HbA1C	hemoglobin A1C
VBG	vertical banded gastroplasty
GB	gastric banding
JIB	jejunoileal bypass
BPD	biliopancreatic diversion
BMI	body mass index
OGTT	oral glucose tolerance test
HGP	hepatic glucose production
HOMA-IR	homeostasis model assessment for insulin resistance
QUICKI	quantitative insulin sensitivity check index
IVGTT	intravenous glucose tolerance test
PYY	peptide YY
IGT	impaired glucose tolerance
FSIVGTT	frequently sampled intravenous glucose tolerance test
AUC	area under the curve
IT	ileal interposition
GK	Goto-Kakizaki
GJB	gastrojejunal bypass
DJB	duodenal-jejunal bypass
GJ	gastrojejunostomy

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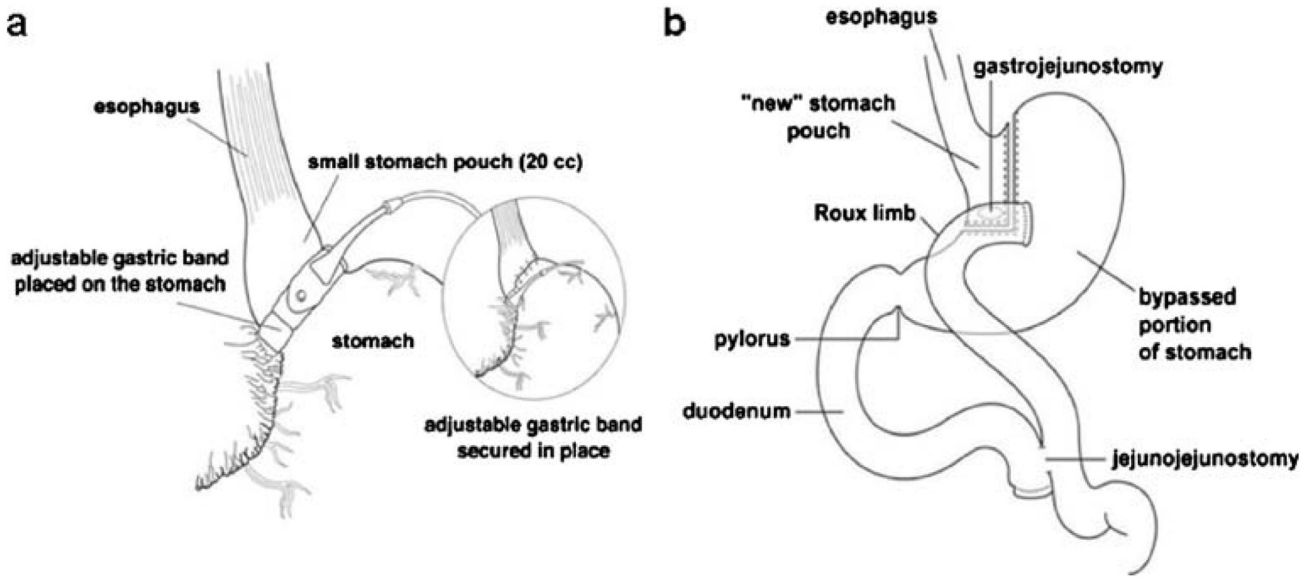

Fig. 1.

Schematic representation of gastric banding (**a**) and gastric bypass (**b**). Graphics courtesy of Packard Children's Hospital, Palo Alto, CA, USA

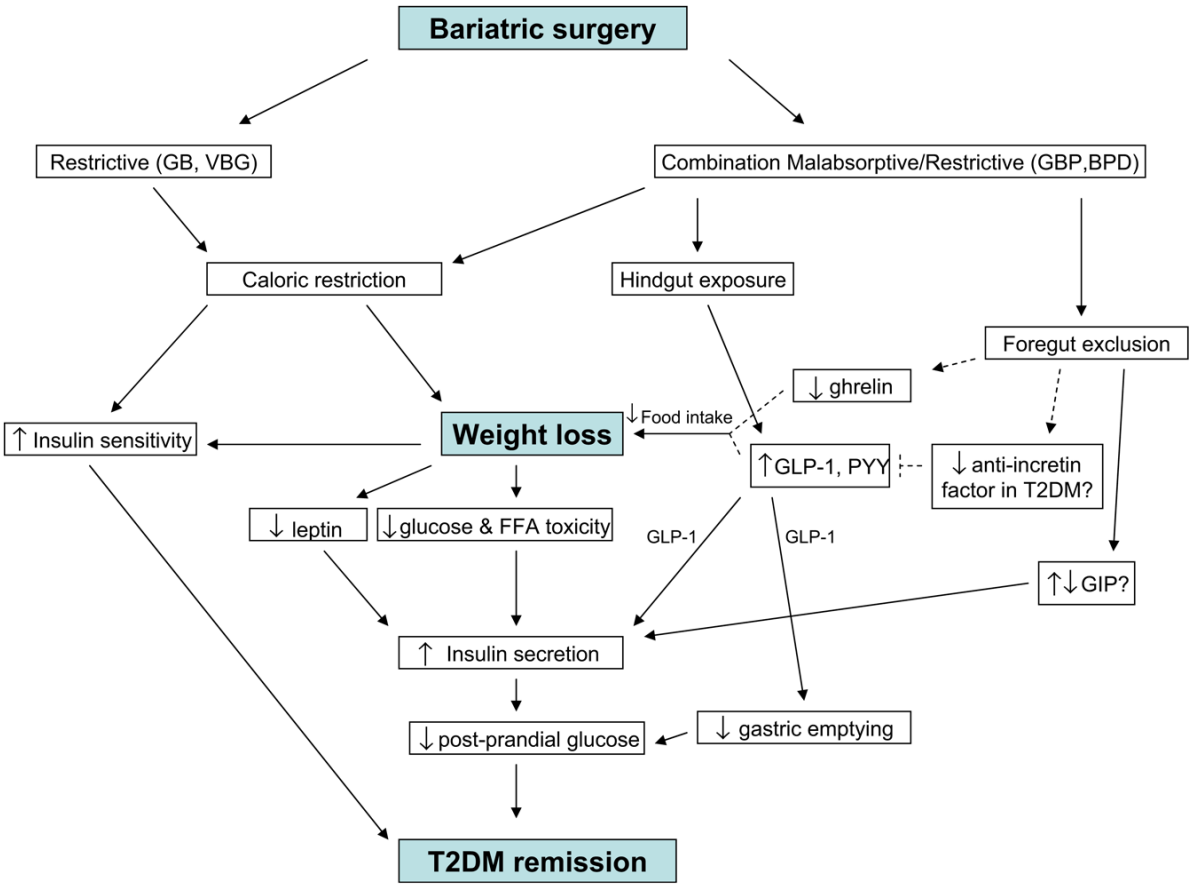

Fig. 2.

Proposed model for mechanisms of T2DM remission after GBP based on available studies. *Dashed lines* indicate hypothetical links

Table 1

Resolution of T2DM after bariatric surgery

Reference	Surgery type	Follow-up duration	Diabetes outcome
Pories et al. [137]	Greenville gastric bypass (*n*=101 with T2DM)	1–10 years	↓ FBG, insulin, HbA1c, ↑ insulin release, glucose disappearance by 1 year
Poulos et al. [138]	GBP (*n*=29 with T2DM)	>1 year	↓ FBG, insulin, HbA1c
Sjostrom et al. [55]	GBP, GB, or VBG (*n*=195 with diabetes)	6–24 months	↓ Incidence of diabetes as defined by ↓ FBG and no medication usage
Pontirolli et al. [57]	GB (*n*=46 with T2DM)	1–3 years	↓ FBG, insulin, HbA1c, HOMA-IR, insulin resistance, glucose tolerance by 1 year
Schauer et al. [139]	GBP (*n*=191 with T2DM)	20 months	↓ FBG, HbA1c, diabetes medication usage by 6 months
Polyzogopoulou et al. [85]	BPD-GBP (*n*=12 with T2DM)	3–12 months	↓ FBG, fasting insulin, ↑insulin sensitivity, AIR by 3 months
Diniz et al. [140]	GBP (*n*=31 with T2DM)	27 months	↓ FBG, HbA1c
Clements et al. [63]	GBP (*n*=20 with T2DM)	2–12 weeks	↓ FBG by 2 weeks
Rubino et al. [61]	GBP (*n*=6 with T2DM)	3 weeks	↓ FBG, insulin
Wickremesekera et al. [86]	GBP (*n*=31 with T2DM)	6 days to 12 months	↓ FBG, ↓ HOMA-IR by 6 days
Guidone et al. [66]	BPD (*n*=10 with T2DM)	4 weeks	↓ FBG, insulin, ↑glucose tolerance, insulin sensitivity, β-cell glucose sensitivity
Mari et al. [87]	BPD (*n*=11 with T2DM)	5 months	↑ glucose tolerance, insulin secretion, insulin sensitivity, β-cell glucose sensitivity
Morinigo et al. [68]	GBP (*n*=11 with T2DM)	6–12 months	↓ FBG, HbA1c, ↑ HOMA-IR,and insulin sensitivity
Alexandrides et al. [141]	GBP (*n*=26 with T2DM)	27 months	↓ FBG
Alexandrides et al. [141]	BPD-RYGBP (*n*=111 with T2DM)	2 years	↓ FBG
DePaula et al. [6]	Ileal interposition with sleeve gastrectomy (*n*=23 with T2DM)	7 months	↓ FBG, fasting insulin, HOMA-IR, HbA1c, ↑ glucose tolerance
DePaula et al. [6]	Ileal interposition with diverted sleeve gastrectomy (*n*=16 with T2DM)	7 months	↓ FBG, fasting insulin, HOMA-IR, HbA1c, ↑ glucose tolerance
Briatore et al. [96]	BPD (*n*=9 with T2DM)	1 month	↓ FBG, HOMA-IR, ↑AIR
Dixon et al. [5]	GB (*n*=30 with T2DM)	2 years	↓ FBG, insulin, HOMA-IR, HbA1c
Brancatisano et al. [56]	GB (*n*=78 with T2DM)	1 year	↓ FBG, HbA1c, diabetes medication usage

T2DM type 2 diabetes mellitus, *FBG* fasting blood glucose, *HbA1c* hemoglobin A1c, *GBP* gastric bypass, *GB* gastric banding, *VBG* vertical banded gastroplasty, *HOMA-IR* homeostasis model assessment of insulin resistance, *BPD* biliopancreatic diversion, *AIR* acute insulin response

Table 2

Longitudinal studies on the effects of bariatric surgery on incretin levels

Reference	Population	Surgery type	Follow-up duration	Outcome
Barry et al. [58]	>300 lb, *n*=12	JIB	3–6 weeks	↑ Fasting EG by 3 weeks ↑ Postprandial EG by 6 weeks
Jorde et al. [77]	*n*=5	JIB	2–6 weeks	↓ Postprandial GIP
Schrumpf et al. [142]	*n*=9	GBP	3–12 months	No change in GIP levels at 3 or 12 months
Sirinek et al. [76]	*n*=12	GBP	3–4 months	↓ Fasting, postprandial GIP
Kellum et al. [59]	*n*=9	GBP	11 months	↑ Postprandial EG
Kellum et al. [59]	*n*=7	VBG	11 months	No effect on fasting, postprandial EG
Rubino et al. [61]	*n*=9, 6 with T2DM	GBP	3 weeks	↓ Fasting GIP in T2DM patients only No change in fasting GLP-1
Clements et al. [63]	*n*=20 with T2DM	GBP	2–12 weeks	↓ Fasting GIP by 6 weeks No significant effect in fasting GLP-1
Valverde et al. [65]	*n*=19	BPD	1–6 months	↑ Fasting, postprandial GLP-1by 6 months
Valverde et al. [65]	*n*=12	VBG	1–6 months	No effect on fasting, postprandial GLP-1
Guidone et al. [66]	*n*=10 with T2DM	BPD	1–4 weeks	↓ Fasting, postprandial GIP by 1 week ↑ Fasting, postprandial GLP-1 by 1 week
Morinigo et al. [69]	*n*=9	GBP	6 weeks	↑ Postprandial GLP-1
Morinigo et al. [68]	*n*=34	GBP	6 weeks, 12 months	↑ Postprandial GLP-1 by 6 weeks
Borg et al. [70]	IR, *n*=6	GBP	1–6 months	↑ Postprandial EG, GLP-1 by 6 months
le Roux et al. [71]	*n*=16	GBP	2–42 days	↑ Postprandial GLP-1 by 2 days
Laferrere et al. [64]	*n*=8 with T2DM	GBP	1 month	↑ Postprandial GLP-1, GIP ↑ IE
Reinehr et al. [67]	*n*=19	GBP	2 years	↓ Fasting GLP-1
Whitson et al. [143]	*n*=10, 5 with T2DM	GBP	6 months	↑ Nonfasted GLP-1 in T2DM only
Laferrere et al. [62]	*n*=9 with T2DM	GBP	1 month	↑ Postprandial GLP-1, GIP ↑ IE
Shak et al. [75]	*n*=24	GB	6–12 months	No change in GLP-1, GIP

JIB jejunoileal bypass, *EG* enteroglucagon, *GIP* gastric inhibitory peptide, *VBG* vertical banded gastroplasty, *T2DM* type 2 diabetes mellitus, *GBP* gastric bypass, *GLP-1* glucagon-like peptide-1, *BPD* biliopancreatic diversion, *IR* insulin resistant, *IE* incretin effect, *GB* gastric banding