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Comparison of Bariatric Surgical Procedures for Diabetes Remission: Efficacy and Mechanisms

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Abstract

Bariatric surgery induces a mean weight loss of 15–30% of initial body weight (depending on the procedure), as well as a 45–95% rate of diabetes remission. Procedures that induce greater weight loss are associated with higher rates of diabetes remission. Improvements in glucose homeostasis after bariatric surgery are likely mediated by a combination of caloric restriction (followed by weight loss) and the effects of altered gut anatomy on the secretion of glucoregulatory gut hormones.

Obesity, which afflicts 35.9% of U.S. adults, dramatically increases the risk of type 2 diabetes.^{1,2} More than two-thirds of the 23 million U.S. adults who have type 2 diabetes are obese.^{3,4} Nutrition therapy, exercise, and medical management remain the cornerstones of both obesity and diabetes treatment, but the long-term success of lifestyle modification has been modest.⁵

Bariatric surgery is currently the most effective therapy for producing mean long-term (10-year) weight losses of 15% of initial body weight, and such weight losses are associated with significant reductions in the incidence of comorbid conditions such as type 2 diabetes.⁵ In 2009, > 220,000 bariatric surgery procedures were performed in the United States alone.⁶ Given its dramatic effects on glucose homeostasis, bariatric surgery has garnered increasing interest as a potential treatment for type 2 diabetes.^{7–9}

Note of disclosure: Dr. Sarwer has served as a paid consultant for Allergan, BAROnova, EnteroMedics, and Ethicon Endo-Surgery, which are manufacturers of products for bariatric surgery. He is also on the board of directors of the Surgical Review Corporation, which created the International Center of Excellence for Bariatric Surgery program to evaluate bariatric surgeons and hospitals around the world and also manages these bariatric Center of Excellence programs on behalf of several bariatric surgery professional societies.

Types of Bariatric Procedures

As shown in Figure 1, several bariatric procedures are currently available.⁹ These procedures were initially classified as restrictive, malabsorptive, or combined (based on their purported mechanism of weight loss), but recent evidence suggests that the mechanisms for each type are less clear than originally thought and likely involve multiple pathways.¹⁰ Bariatric surgeries are now more broadly classified as: 1) restrictive procedures, which dramatically reduce the volume of the stomach to limit gastric capacity and promote early satiety but do not alter intestinal anatomy; or 2) gastrointestinal (GI) diversionary procedures, which bypass segments of the small bowel.¹¹

Restrictive procedures

Adjustable gastric banding (AGB), in which an inflatable silicone band is placed around the fundus of the stomach, is believed to be the most commonly performed restrictive procedure worldwide.¹² In this procedure, the GI anatomy remains intact, and the rate of gastric emptying is not altered.¹³

As recently as 2009, AGB accounted for 40% of bariatric procedures performed in the United States.¹⁴ However, AGB is rapidly being supplanted by vertical sleeve gastrectomy (VSG), a newer restrictive procedure that removes 75% of the stomach, including virtually all of the hormonally rich gastric fundus.⁵ Although VSG is conceptually a restrictive procedure, the removal of endocrine-rich gastric tissue and the accelerated rate of gastric emptying^{15,16} caused by this procedure is hypothesized to have significant physiological implications and may account for its superior efficacy relative to other restrictive procedures.

GI diversionary procedures

Roux-en-Y gastric bypass (RYGB), the most commonly performed GI diversionary procedure, restricts gastric size and bypasses the entire duodenum and the proximal jejunum.¹⁷ RYGB accounts for ~ 50% of bariatric surgeries performed worldwide.¹² Biliopancreatic diversion (BPD) is a more extensive surgical procedure that includes a partial gastrectomy and bypasses a longer segment of the small bowel to induce significant malabsorption.¹⁷ BPD accounts for only 5% of bariatric procedures performed in the United States and is usually reserved for patients who have a BMI > 50 kg/m².¹⁷ Detailed descriptions of these procedures are provided in Table 1.⁵

Effect of the Procedures on Weight Loss

Typically, procedures that induce greater weight loss are associated with higher rates of diabetes remission.¹⁸ However, comparison of bariatric data has been difficult because of a lack of standardization in reporting weight loss.^{7,19-22} In the surgical literature, weight loss is typically expressed as a percentage of excess weight lost (EWL), in which excess weight is defined as total preoperative weight minus ideal weight.¹⁸ The percentage of EWL is thus defined as $\text{weight loss/excess weight} \times 100$. The percentage change in total weight and percentage change in BMI after bariatric surgery have also been reported.¹⁸⁻²²

In a meta-analysis, Buchwald et al.²² evaluated the effect of bariatric surgery on weight loss and obesity-related comorbidities in 135,246 patients. An overall EWL of 55.9% was reported for all procedures, whereas individual rates associated with each procedure varied (Table 2). On average, bariatric surgery has been found to result in a BMI reduction of 10-15 kg/m² and a weight loss of 30-50 kg.^{18,19}

Two randomized, controlled trials reported greater weight loss with RYGB than with AGB.^{23,24} A recent trial that included 250 participants randomly assigned to RYGB or AGB reported a mean percentage of EWL of 68.4 and 45.4%, respectively, 4 years after surgery.²⁴ These results were similar to those of an earlier, smaller, randomized trial that provided 5 years of follow-up, in which the mean EWL was 66.6% in participants who underwent RYGB and 47.5% in those who underwent AGB.²³

Although VSG and AGB are both classified as restrictive procedures, VSG appears to induce superior weight loss compared to AGB. One randomized trial that compared the magnitude of weight loss between the two procedures at 1 and 3 years found that AGB resulted in an EWL of 41.4 and 48%, respectively, versus 57.5 and 66%, respectively, for VSG.²⁵ Two randomized trials reported comparable short-term weight loss between VSG and RYGB at 3 months²⁶ and 12 months.²⁷ In a randomized trial that compared the long-term efficacy of VSG and RYGB on weight outcomes, Kehagias et al.²⁸ also reported comparable weight loss between the two procedures at 3 years (68 vs. 62% of EWL, respectively).

Maximal weight loss is typically achieved 12-18 months after all procedures,²¹ although evidence suggests that some patients regain a significant amount of weight several years after surgery.²⁹ Ten-year follow-up from the Swedish Obese Subjects (SOS) study, a prospective cohort study that included 4,047 obese participants who underwent a variety of bariatric surgery procedures or nonsurgical conventional management, found that each procedure was associated with significant weight regain.²⁹ Mean weight loss decreased in the RYGB group from 32% at 1 year to 25% at 10 years, in the gastric banding group from 20 to 13%, and in the group treated with vertical banded gastroplasty (a restrictive procedure now rarely performed) from 25 to 18%. For all procedures, substantial weight loss was nonetheless sustained at a greater level than that achieved with nonsurgical weight loss interventions.

Definitions of Diabetes Remission

There is considerable heterogeneity among definitions of diabetes remission, which hinders comparison of remission rates among various surgical studies. Diabetes remission is often broadly defined as “normal” fasting blood glucose and A1C values without the use of antidiabetic medications.¹⁸ However, this definition does not include specific criteria for A1C levels (cut-offs have varied from < 6.0 to 7.0% in the surgical literature), a quantifiable timeframe for which antidiabetic medications must be discontinued, or more rigorous measures of assessment (e.g., oral glucose tolerance testing).

In response to a growing demand for a standardized definition of diabetes remission, a consensus group consisting of experts in pediatric and adult endocrinology, bariatric/metabolic surgery, transplantation, metabolism, and hematology-oncology was convened by the American Diabetes Association (ADA) in 2009.³⁰ “Partial remission” was defined as mild hyperglycemia (fasting glucose levels of 100-125 mg/dl and A1C levels of < 6.5%) for at least 1 year in the absence of active pharmacological therapy or ongoing procedures. “Complete remission” was defined as a return to normal measures of glucose metabolism (fasting glucose levels of < 100 mg/dl and A1C levels < 6.0%) for at least 1 year in the absence of active pharmacological therapy or ongoing surgical procedures such as repeated replacement of endoluminal devices. “Prolonged remission” was defined as complete remission for at least 5 years’ duration. The group was unable to reach a consensus on the value of oral glucose tolerance testing in defining remission.

Evidence Regarding Diabetes Remission from Bariatric Surgery

Observational evidence suggests that bariatric surgery is associated with a 45-95% rate of diabetes remission, depending on the type of procedure.^{18,22,31} In the largest meta-analysis to date,²² which included 3,188 patients with type 2 diabetes who underwent bariatric surgery, the disease resolved in 78% and resolved or improved in 87%. Weight loss and diabetes remission were greatest for BPD, followed by RYGB, and then AGB (Table 2). VSG was not included in this meta-analysis because it was not a commonly performed bariatric procedure at the time.

Among studies that included exclusively diabetic patients, the rate of clinical and biochemical remission of diabetes in the first 2 years after surgery was 82%. Sixty-two percent remained free of diabetes > 2 years after surgery. However, many of the studies in this meta-analysis had significant methodological limitations. Therefore, cautious interpretation of conclusions about bariatric surgery and diabetes remission is advised. Few of the studies were randomized, controlled trials, and many were uncontrolled case series with significant amounts of missing data. Participants were not always enrolled consecutively, and heterogeneous outcomes were used to define diabetes remission.

Using the more stringent definition recommended by the ADA consensus group, Pournaras et al.³² retrospectively compared rates of diabetes remission in 209 subjects with type 2 diabetes who underwent RYGB, VSG, and AGB at three bariatric centers in the United Kingdom. Mean follow-up was 23 months (range 12-75 months). A total of 72 (34.4%) had complete remission of diabetes according to the new definition. The remission rates were 40.6% after RYGB, 26% after VSG, and 7% after AGB ($P < 0.001$ between groups). The remission rate for RYGB was significantly lower with the new definition than with the previously used definition (40.6 vs. 57.5%, $P = 0.003$).

Trials Comparing Diabetes Remission Rates From Bariatric Surgery and Intensive Medical Management

In response to increasing demand for high-quality studies comparing the diabetes remission rates of bariatric surgery and medical management, several randomized, controlled trials have recently been completed.

Dixon et al.³³ randomized 60 obese participants with BMIs of 30-40 kg/m² and a recent diagnosis of type 2 diabetes (< 2 years) to either AGB or conventional medical therapy. The primary endpoint was the rate of diabetes remission at 2 years, defined as a fasting glucose of < 126 mg/dl and an A1C of < 6.2% in the absence of anti-diabetic medications. Conventional medical therapy consisted of visits every 6 weeks with at least one member of the medical team, which included a general physician, nurse, diabetes educator, and dietitian, for the duration of the trial. Pharmacological therapy was determined on an individual basis by a diabetologist, and all participants in this group received individual counseling about lifestyle modification. Fifty-five participants (92%) completed follow-up at 2 years. Twenty-two of 30 participants (73%) in the surgical group achieved the primary endpoint compared to 4 of 30 (13%) in the medical therapy group. Surgical and conventional therapy groups lost a mean of 20.7 and 1.7% of initial body weight, respectively.

In the recently completed STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial, Schauer et al.³⁴ randomly assigned 150 obese participants with poorly controlled type 2 diabetes (A1C > 7.0%) to one of three interventions: 1) intensive medical management alone, 2) RYGB, or 3) VSG, with intensive

medical therapy as an adjunct to both surgical procedures. The primary endpoint was defined as the proportion of participants with an A1C $\leq 6.0\%$ at 12 months. All participants received intensive medical therapy per ADA guidelines, including lifestyle counseling, weight management, frequent self-monitoring of blood glucose, and use of newer glycemic therapies such as incretin mimetics.

Of the 150 participants, 140 (93%) completed follow-up at 12 months. Twenty-one of 50 participants (42%) in the RYGB group achieved the primary endpoint, compared to 18 of 49 (37%) in the VSG group, and 5 of 41 (12%) in the medical management group. All participants in the RYGB group achieved the target A1C without antidiabetic medications, whereas 5 of 18 (28%) in the VSG required one or more glucose-lowering drugs. In contrast, the use of antidiabetic medications increased in the medical management group. The mean percentage of weight loss among participants undergoing either RYGB or VSG (25.7 and 24.7%, respectively) was significantly greater than for those undergoing medical therapy (5.2%, $P < 0.001$ for both comparisons).

Mingrone et al.³⁵ randomly assigned 60 participants with a BMI ≥ 35 kg/m² and a history of type 2 diabetes for ≥ 5 years to undergo RYGB, BPD, or standard medical therapy. The primary endpoint was the rate of diabetes remission at 2 years (defined as a fasting glucose of < 100 mg/dl and an A1C of $< 6.5\%$ without antidiabetic medications). Standard medical therapy consisted of visits (at baseline and months 1, 3, 6, 9, 12, and 24) with a multidisciplinary team that included a diabetologist, dietitian, and nurse. Pharmacological therapy was optimized on an individual basis, and a lifestyle modification program was provided, although the specific nature of this program was not described.

Fifty-six participants (93%) completed the 2-year follow-up. Remission was achieved by 75% in the RYGB group and 95% in the BPD group. No participants in the medical therapy group achieved remission. At 2 years, participants in the two surgical groups had significantly greater percentage reductions in mean body weight than those in the medical therapy group (33.3% for RYGB and 33.8% for BPD, compared to 4.7% for the control group; $P < 0.001$ for both comparisons).

Importantly, all three of these studies used intensive medical management rather than routine care as the control. The weight loss that was achieved in the medical management groups in these studies was comparable to that reported in three recent randomized trials in which intensive weight loss interventions were delivered within primary care practices.³⁶⁻³⁸ At 2 years, weight loss in the intensive treatment arms in these studies ranged from 1.7 to 5.2%.

Predictors of Diabetes Remission

If bariatric surgery is to be considered a potential treatment for type 2 diabetes, it is crucial to identify preoperative predictors of remission to help determine which patients will benefit the most from surgery. After adjusting for BMI, sex, and preoperative A1C level, Torquati et al.³⁹ found that preoperative treatment with oral antidiabetic agents (as opposed to insulin) and smaller preoperative waist circumference predicted diabetes remission. Two studies reported that patients with longstanding diabetes (> 10 years), preoperative insulin use, and poor preoperative glycemic control were less likely to achieve diabetes remission.^{40,41} However, these studies did not control for important confounding factors that may also influence diabetes remission, including age, sex, preoperative BMI, and preoperative A1C level. Eating behaviors and eating habits have been associated with weight loss after bariatric surgery.⁴² However, it is unknown whether these variables also may be associated with diabetes remission, particularly over long periods of time.

Potential Mechanisms for Improved Glycemic Control After Bariatric Surgery

Caloric restriction

All bariatric procedures induce significant reductions in caloric intake in the early postoperative period, and the beneficial effect of caloric restriction on glycemia is well established.⁴³ To determine whether caloric restriction ipso facto accounts for the immediate improvement in glycemic parameters within the first week of RYGB (before weight loss), Isbell et al.⁴⁴ compared the metabolic response to a mixed-nutrient meal in nine participants before and after RYGB (an average of 4 days postoperatively) and nine matched obese control subjects before and after 4 days of the postoperative diet. Half of the participants in each group had type 2 diabetes.

Participants who underwent caloric restriction comparable to those in the RYGB group displayed similar changes in meal-stimulated glucose and insulin sensitivity after 4 days on an isocaloric diet. The potent insulin secretagogue glucagon-like peptide 1 (GLP-1) increased significantly after RYGB but remained unchanged in the calorie-restricted group.

Because a comparable improvement in glucose tolerance and insulin sensitivity was observed after caloric restriction without alterations in the incretin response, these data suggest that decreased caloric intake alone accounts for the rapid improvement in glycemia after surgery. However, it is important to note that the groups were clinically (although not statistically) different at baseline with respect to weight (153.2 ± 32.2 kg in the RYGB group versus 127.0 ± 36.5 kg in the diet group), and the confounding effects of type 2 diabetes and weight were inadequately adjusted for given the small sample size.⁴⁵ Furthermore, use of insulin and other antidiabetic medications was not reported, which limits the generalizability of these findings.⁴⁵

Weight loss

Weight loss is one of the predominant mechanisms by which bariatric surgery induces diabetes remission, as demonstrated in multiple studies that have shown higher rates of diabetes remission with greater weight loss.^{17,22,29,33} Studies of AGB provide, perhaps, the strongest evidence for the role of weight loss in diabetes remission because improvements in glucose homeostasis occur independently of changes in the secretion of glucoregulatory gut hormones. In the landmark study by Dixon et al.³³ described above, remission of type 2 diabetes was strongly related to weight loss.

Changes in the enteroinsular axis

Significant anatomical differences exist between AGB, VSG, and procedures that bypass segments of the gut (RYGB and BPD), resulting in distinctly different effects on the secretion of the incretin hormones GLP-1 and glucose-dependent insulintropic polypeptide (GIP), the satiety factor peptide YY (PYY), and the orexigenic hormone ghrelin. These neuroendocrine factors are secreted by the gut mucosa in response to ingestion of nutrients, neural signals, and nutrient sensing.⁴⁶ Many of these peptides influence glycemic control by modulating insulin secretion and possibly insulin sensitivity. The incretin effect is blunted in obese individuals with type 2 diabetes, which may contribute to impaired glucose homeostasis.⁴⁶

Because AGB leaves the GI tract intact and does not significantly alter the rate of gastric emptying,¹³ changes in the secretion of gut hormones occur in response to weight loss only and are less pronounced than changes after malabsorptive or combined procedures.¹⁰ RYGB excludes the proximal gut and thus expedites nutrient delivery to the distal ileum, resulting

in altered secretion of the enteroendocrine factors described in more detail below.¹⁷ Similar changes in the secretion of gut peptides are observed after BPD¹⁵ and VSG^{26,45} because gastric emptying is accelerated after both procedures.^{15,16} Table 3 offers a summary of the effect of the various bariatric procedures on glucoregulatory gut peptides. Table 4 summarizes the roles these hormones play in influencing appetite and satiety.

GLP-1—This incretin hormone, a potent satiety signal and insulin secretagogue, is secreted by the L cells of the distal ileum in response to nutrients and neural signals arising from the proximal gut.⁴⁶ GLP-1 acts directly on pancreatic β -cells to enhance glucose-dependent insulin secretion. It also suppresses glucagon secretion, although the mechanism for this has not been clearly elucidated.⁴⁶ GLP-1 attenuates postprandial glycemia by slowing gastric emptying and exerts additional effects on the central nervous system to induce satiety and decrease food intake.⁴⁶

Basal levels and the postprandial response of GLP-1 are reduced in obese individuals with type 2 diabetes.⁴⁷ Despite the reduced concentration, GLP-1 function remains intact in patients with diabetes when levels are restored.⁴⁸

Multiple studies of RYGB and BPD have demonstrated a markedly enhanced GLP-1 response after these two procedures.⁴⁹⁻⁵⁴ Such a response appears to be independent of weight loss itself. Laferrère et al.⁵² demonstrated a sixfold increase in the postprandial GLP-1 response in obese, diabetic participants who had undergone RYGB, whereas the GLP-1 response was unchanged in matched obese, diabetic control subjects who had lost an equivalent amount of weight on a hypocaloric diet. Moreover, GLP-1 levels remain persistently elevated after RYGB, with levels increased at least 1 year after surgery.⁵⁰

Because rapid gastric emptying occurs after VSG, the GLP-1 response is also enhanced. One randomized trial that compared the effects of RYGB versus VSG on glucose metabolism reported significant increases in postprandial GLP-1 levels at 1 week and 3 months after both procedures. However, this increased response for GLP-1 was greater with RYGB than with VSG at both time points, as measured by the area under the curve.⁵⁵ In contrast, GLP-1 levels are not altered by AGB, in part because the rate of gastric emptying is not altered. Korner et al.⁵¹ showed that postprandial GLP-1 levels increased threefold after RYGB but remained unchanged after gastric banding.

The physiological activity of GLP-1 has been extensively investigated through blockade of its receptor by exendin 9-39-amide (Ex-9).⁵⁶⁻⁶⁰ Ex-9 completely eliminates the effect of endogenous GLP-1 on postprandial insulin release but has no effect on other hormones that enhance insulin secretion.⁵⁸⁻⁶⁰ Kindel et al.⁶¹ found that diabetic rats that underwent duodenal-jejunal exclusion (a procedure that simulates the GI diversion of RYGB but does not induce weight loss) had significant improvement in glucose tolerance compared to sham-operated rats. However, infusion of Ex-9 attenuated the improvement in glucose tolerance, suggesting that GLP-1 directly improves glucose homeostasis in rodents after a gastric bypass-like procedure.

Extending these findings to human subjects, Salehi et al.⁶² used Ex-9 to determine whether RYGB-associated hyperinsulinism is mediated by enhanced GLP-1 action and whether this accounts for greater β -cell stimulation in subjects with postsurgical hypoglycemia.⁶² The administration of Ex-9 reduced postprandial insulin secretion rates by 33% in individuals who had undergone RYGB, compared to 16% in BMI-matched control subjects, demonstrating that GLP-1 has a heightened effect on postprandial insulin release after RYGB.

GIP—This incretin hormone is secreted by the K cells of the proximal gut in response to the ingestion of carbohydrates and lipids. Although less potent than GLP-1, GIP also acts on pancreatic β -cells to augment postprandial insulin secretion.⁶³ Unlike GLP-1, GIP does not have any effect on the rate of gastric emptying or satiety. Data from studies examining GIP levels in individuals with type 2 diabetes remain discrepant, with some investigators reporting unchanged⁶⁴ or even increased levels of this hormone.⁶⁵ However, multiple studies have consistently demonstrated that the insulinotropic activity of GIP is impaired in type 2 diabetes.⁶⁶⁻⁶⁸

The response of GIP to bariatric surgery has been more variable than that of GLP-1. Several studies^{52,69} have reported that GIP levels are reduced after RYGB, possibly as a result of reduced stimulation of the K cells in the proximal gut as a consequence of the bypass. In contrast, Laferrère et al.⁵⁰ reported a transient elevation in GIP levels 1 month after RYGB, but this response was not sustained. Näslund et al.⁷⁰ reported persistent elevations in GIP levels up to 20 years after jejunoileal bypass. Like RYGB, this procedure causes early delivery of nutrient-rich chyme to the distal small intestine.

Few studies have evaluated the effect of restrictive procedures on GIP concentrations. Two observational studies^{51,71} reported no change in GIP levels 6, 12, and 24 months after AGB. To date, no studies have examined the effect of VSG on the GIP response.

PYY—This peptide is a satiety signal that is cosecreted with GLP-1 from the L cells of the distal ileum in response to nutrients.⁷² In addition to decreasing appetite through central mechanisms,⁷³ PYY indirectly affects glucose homeostasis through activation of melanocortin neurons in the hypothalamus that affect insulin sensitivity.⁷⁴

Procedures such as RYGB that expedite nutrient delivery to the distal ileum result in an exaggerated PYY response to nutrient ingestion.^{75,76} Korner et al.⁷⁵ reported a tenfold increase in postprandial PYY concentrations following RYGB, compared to the response observed in lean and obese nonsurgical control subjects. There have also been reports that PYY levels increase after VSG, but the response appears to be transient. In a randomized trial, Karamanakos et al.⁵⁵ found that VSG and RYGB resulted in comparable increases in PYY levels for the first 6 months after surgery. However, the secretion of PYY was significantly reduced by 12 months in the VSG group, whereas the response was maintained in the RYGB group. The authors speculated that reduced PYY secretion was the result of physiological adaptation of the gastric remnant over time. Because AGB does not alter the rate of gastric emptying, the PYY response remains unchanged after this procedure.⁷⁵

Ghrelin—This orexigenic hormone is primarily secreted by the gastric fundus and proximal small intestine and acts on the hypothalamus to stimulate appetite.¹⁰ This hormone and its receptor are also expressed in pancreatic islet cells.¹⁰ Ghrelin is known to inhibit insulin secretion, possibly through an autocrine or paracrine mechanism that has yet to be elucidated.⁷⁷

The role of ghrelin in diabetes remission after bariatric surgery remains controversial. Ghrelin contributes to the marked loss of appetite and reduction in food intake that mediates weight loss after certain procedures and is known to enhance insulin sensitivity. Because ghrelin inhibits insulin secretion, suppresses the insulin-sensitizing hormone adiponectin, and stimulates the release of counterregulatory hormones,⁷⁸ a reduction in ghrelin secretion may have beneficial effects on glucose homeostasis.

The effects of gastric bypass on ghrelin levels are inconsistent. Some reports^{79,80} have demonstrated reduced levels of ghrelin after RYGB, whereas others have shown no

change⁸¹ or increased levels.⁸² Sundbom et al.⁸³ reported a transient reduction in ghrelin secretion in the immediate and early postoperative period after RYGB, followed by a gradual increase in ghrelin secretion as weight loss ensued.

Variations in surgical techniques may account for these discrepant findings.¹⁰ If a small amount of gastric ghrelin-producing tissue is left intact, the residual cells can compensate to maintain normal ghrelin secretion. Ghrelin secretion is also affected by the vagus nerve, which is sometimes intentionally severed during RYGB. Ghrelin levels are typically higher after procedures such as AGB that maintain vagal integrity.

Because a significant amount of the gastric fundus is removed in VSG, ghrelin levels are significantly reduced after this procedure.²⁶ In a randomized, controlled trial, fasting and postprandial ghrelin levels were found to be lower in participants who underwent VSG than in those who underwent RYGB.²⁶

Hindgut versus foregut hypotheses

Two possible theories have been proposed to explain the rapid improvement in glucose homeostasis after gastric bypass. The hindgut hypothesis suggests that the expedited delivery of nutrients to the distal ileum (as a result of the shortened length of the small bowel) improves glycemia through the enhanced secretion of gut peptides such as GLP-1, which augments glucose-dependent insulin secretion.⁸⁴ In contrast, the foregut hypothesis suggests that the exclusion of the proximal bowel (as a consequence of GI rearrangement) prevents the secretion of an unidentified “putative signal” that promotes insulin resistance and type 2 diabetes.⁸⁴ Existing data from both animal and human studies lend support to both the foregut⁸⁵⁻⁸⁸ and hindgut theories,⁸⁹⁻⁹² but the predominant mechanism of improved glucose metabolism has yet to be elucidated.

Effects of Bariatric Surgery on Insulin Sensitivity

Bariatric surgery affects both insulin secretion and insulin sensitivity, which are related in a hyperbolic manner such that compensatory increase in one induces a subsequent reduction in the other.⁹³ Although it is well established that insulin sensitivity substantially improves in response to weight loss,⁴² some of the procedures may also enhance insulin sensitivity independent of weight loss.

The mechanisms underlying improved glucose homeostasis after bariatric surgery have been most intensively studied in participants who have undergone BPD.⁹⁴⁻⁹⁶ Mari et al.⁹⁵ reported a significant increase in insulin sensitivity, as measured by the gold standard hyperinsulinemic-euglycemic clamp methodology, within days of BPD in a group of obese patients with glucose tolerance levels ranging from normal to frank diabetes. Insulin sensitivity did not improve in a matched obese control group with a similar metabolic profile who had undergone abdominal surgery for reasons other than BPD (mainly cholecystectomy and abdominal hernia repair), despite equivalent caloric restriction. This suggests that the improved glucose homeostasis after BPD occurred independent of weight loss and reduced food intake. Other studies have shown normalization of insulin-mediated, whole-body glucose uptake after BPD (often in excess of normal values) when compared to lean individuals, suggesting that this procedure confers supranormal insulin sensitivity.⁹⁶

The short-term effects of RYGB on insulin sensitivity are less clear. Several studies⁹⁷⁻⁹⁹ that used the hyperinsulinemic-euglycemic clamp methodology found no improvement in insulin sensitivity within the first 4 weeks after RYGB. However, these studies were limited by the fact that participants were either nondiabetic or included a mixture of normoglycemic to frankly diabetic participants. In contrast, Kashyap et al.¹⁰⁰ reported enhanced insulin

sensitivity as assessed by a hyperglycemic clamp as early as 1 and 4 weeks after RYGB in an exclusively diabetic study population. Insulin sensitivity was unchanged at both time points in participants who underwent gastric restrictive surgery (AGB or VSG), despite weight losses equivalent to those in the RYGB group.

Because diabetic and nondiabetic individuals may respond differently to the various surgeries, further study using rigorous methodology is needed to better elucidate the short-term effects of bariatric surgery on insulin sensitivity.

Use of Bariatric Surgery for Diabetes Remission in Overweight to Mildly Obese Patients

Given the remarkable rate of diabetes remission with bariatric surgery, there is considerable interest in offering this intervention to diabetic patients with a BMI of $< 35 \text{ kg/m}^2$. Several case series and nonrandomized prospective trials have evaluated the efficacy of various bariatric surgery procedures on diabetes remission in less obese individuals.^{27,101,102} However, most of these studies have been limited by significant methodological limitations, including small sample size, poor follow-up, and heterogeneous criteria for diabetes remission. In a nonrandomized study that included 20 patients with poorly controlled diabetes and a mean BMI of 31 kg/m^2 who underwent VSG, Lee et al.²⁷ reported a 50% diabetes remission rate 52 weeks after surgery. Similar results were reported in a study of AGB performed in diabetic patients with a mean BMI of 33 kg/m^2 .¹⁰¹ In a case series that included 37 obese, diabetic patients with a mean BMI of 32.5 kg/m^2 who underwent RYGB, Cohen et al.¹⁰² reported that diabetes was resolved in all participants after a follow-up of 6-48 months. However, participants in this series had mild diabetes (a mean fasting glucose level of 146 mg/dl on oral medications only), and only nine participants returned for follow-up at 48 months.

A 2009 study¹⁰³ found that, among patients with a BMI of $32\text{-}34 \text{ kg/m}^2$, only the most severe category of diabetes (A1C level of $> 9\%$ on maximal medical therapy) was deemed “appropriate” for bariatric surgery. The expert panel (consisting of 11 bariatric surgeons, two internists, and one endocrinologist) who developed these criteria felt that the current evidence does not support bariatric surgery in individuals with a BMI of $< 32 \text{ kg/m}^2$.

A recent survey study¹⁰⁴ also found guarded enthusiasm among endocrinologists and primary care physicians for the use of bariatric surgery in people with type 2 diabetes and a BMI $< 35 \text{ kg/m}^2$. Only 20.8% of respondents indicated that they would be likely to refer their patients with type 2 diabetes and a BMI of $30\text{-}34.9 \text{ kg/m}^2$ to a randomized research trial of bariatric surgery.

Diabetes Relapse Rate

Evidence from the SOS study suggests that improvement in glycemia and cardiovascular benefits persist for years after bariatric surgery.¹⁰⁵ However, emerging evidence suggests that diabetes does recur in a significant number of patients.^{106,107}

One small study¹⁰⁶ that included 42 patients who had previously undergone RYGB and had 3 years of follow-up found that 10 patients (24%) experienced a relapse of diabetes. In that study, diabetes recurrence was defined as an A1C $> 6.0\%$ and a fasting glucose level $> 125 \text{ mg/dl}$ and/or a requirement for glycemic medication in patients who had previously been in remission. Long-term studies suggest an even higher rate of diabetes relapse. In a case series that followed 157 patients who had previously undergone RYGB and had experienced initial remission of diabetes, 68 (43.1%) experienced a recurrence.¹⁰⁷ Follow-up ranged from 5 to

16 years, and diabetes status was determined by patient interview and evaluation of antidiabetic medications. Both studies found that less initial weight loss and greater weight regain were associated with a greater likelihood of diabetes relapse.^{106,107}

The criteria for diabetes relapse have not been clearly defined.¹⁰⁸ Postprandial hypoglycemia (typically asymptomatic) is relatively common in patients after RYGB. This may have the cumulative effect of falsely lowering A1C levels and masking the early stages of type 2 diabetes relapse.¹⁰⁸ Further long-term studies are needed to assess the durability of diabetes remission and more accurately quantify the rate of relapse.

The issue of diabetes relapse is of particular concern when the use of bariatric surgery is considered for younger adults or adolescents. Consistent with many major academic medical centers in urban areas, the mean age of our patients is 44 years. However, we have recently observed a growing number of individuals in their 30s, many with type 2 diabetes and others with a strong family history of the disease, who are presenting for bariatric surgery with the primary objective of treating or preventing type 2 diabetes. Although surgical interventions may be particularly efficacious in the short term (within the first decade), relapse subsequently may occur and warrant further treatment.

Conclusion

Bariatric surgery induces significant improvements in glucose homeostasis through a number of mechanisms. Diabetes remission rates are highest for procedures that induce the greatest weight loss. Based on meta-analyses, BPD confers the highest rates of remission, followed by RYGB and AGB. Emerging evidence suggests that VSG induces rates of remission that are intermediate between RYGB and AGB.

All bariatric surgery procedures initially induce caloric restriction in the early postoperative period, but the various procedures appear to have differential effects on the secretion of glucoregulatory gut hormones. AGB does not alter the integrity of the GI tract or nutrient transit time and is not associated with changes in the secretion of gut peptides that are known to enhance insulin action. In contrast, VSG, RYGB, and BPD are associated with the enhanced secretion of the incretin hormones, reduced secretion of ghrelin, and greater weight loss. In conjunction, these changes result in reduced hyperinsulinemia and improved insulin sensitivity.

With increasing numbers of diabetic patients undergoing bariatric surgery, long-term randomized clinical trials comparing the effectiveness of surgical and medical therapies for type 2 diabetes are urgently needed. Studies are underway to evaluate the risk-benefit ratio of surgery in individuals with diabetes who meet the present criteria for bariatric surgery, as well as for less obese (BMI 30-35 kg/m²) populations.

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Figure 1. Bariatric and metabolic surgical operations. Reproduced from the National Institute of Diabetes and Digestive and Kidney Diseases Web site (ref. 9).

Table 1Description of Bariatric Surgery Procedures Currently in Use⁵

Procedure	Description	Common Complications	Early Operative Mortality Rate (%)	Effect on Gastric Emptying
Restrictive procedures				
AGB	Inflatable silicone band placed around the gastric fundus to create a 30-cc pouch; gastric anatomy remains intact	Band slippage or band erosion, gastric reflux, esophageal dilatations, and vomiting	0.1 *	No change
VSG	75% of the stomach is removed, including virtually all of the fundus; no rearrangement of small bowel	Leakage, vomiting due to overeating	NA	Accelerated
Gastrointestinal diversionary procedures				
BPD	Partial gastrectomy performed to create a 150- to 200-cc gastric sleeve, which is anastomosed to the small intestine. The excluded portion of the small intestine that serves as the conduit for bile and pancreatic juices is attached 100 cm proximal to the ileocecal valve. In the duodenal switch variation, the gastric antrum, pylorus, and a short portion of the duodenum are left intact.	Anastomotic leakage and ulceration, chronic diarrhea, protein malnutrition, vitamin deficiencies, anemia	1.1	Accelerated
RYGB	Gastrectomy performed to create a 30-cc pouch, to which the distal jejunum is anastomosed. The proximal jejunum is reattached 75–150 cm below the gastro-jejunal anastomosis.	Anastomotic leaks, failure of the staple partition, acute gastric dilatation, vomiting, ulceration, wound hernias, intestinal obstruction, dumping syndrome	0.5	Accelerated

* Rate includes estimates from laparoscopic adjustable gastric band and vertical banded gastroplasty, a restrictive procedure that is now rarely performed.

Table 2Remission and Improvement in Type 2 Diabetes Associated With Various Bariatric Procedures ^{#22}

	AGB	RYGB	BPD
EWL (%)	46.2	59.7	63.6
Remission of type 2 diabetes (%)	56.7	80.3	95.1

*
VSG was not included in this meta-analysis.

Table 3

Overview of Altered Secretion of Gut Peptides in Response to Different Bariatric Procedures

	AGB	VSG	RYGB	BPD
Ghrelin	Increase	Decrease	Increase/decrease (variable)	Decrease
GLP-1	No change	Increase	Increase	Increase
GIP	No change	Unknown	Increase/decrease (variable, but most studies report reduced levels)	Decrease
PYY	No change	Increase	Increase	Increase

Table 4**Roles of Hormones Influencing Appetite and Satiety**

	Primary Action	Additional Effects on Glucose Homeostasis	Released by	Target
Ghrelin	Stimulates appetite	Inhibits insulin secretion, inhibits adiponectin (an insulin-sensitizing hormone)	Primarily secreted by the gastric fundus, but small concentrations also released by the proximal small intestine, liver, pancreas, kidney, lung, and other organs	Hypothalamus, pancreatic islet cells
GLP-1	Stimulates postprandial insulin release	Suppresses glucagon secretion, suppresses endogenous glucose production, delays gastric emptying to attenuate postprandial hyperglycemia, and induces satiety	L cells of distal ileum (in response to nutrients)	Multiple organs (pancreatic islet cells, liver, heart, lungs, and hypothalamus)
GIP	Stimulates postprandial insulin release (but is less potent than GLP-1)	Stimulates glucagon secretion	K cells of proximal gut (in response to nutrients)	Pancreatic islet cells
PYY	Induces satiety	Delays gastric emptying to attenuate postprandial hyperglycemia	Produced mainly by the L cells of distal ileum (in response to nutrients), but can also be secreted by other endocrine cells and neurons of the central nervous system	Melanocortin neurons in the hypothalamus