The Effects of Bariatric Surgery on Islet Function, Insulin Secretion, and Glucose Control

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ABSTRACT Although bariatric surgery was developed primarily to treat morbid obesity, evidence from the earliest clinical observations to the most recent clinical trials consistently demonstrates that these procedures have substantial effects on glucose metabolism. A large base of research indicates that bariatric surgeries such as Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG), and biliopancreatic diversion (BPD) improve diabetes in most patients, with effects frequently evident prior to substantial weight reduction. There is now unequivocal evidence from randomized controlled trials that the efficacy of surgery is superior to intensive life-style/medical management. Despite advances in the clinical understanding and application of bariatric surgery, there remains only limited knowledge of the mechanisms by which these procedures confer such large changes to metabolic physiology. The improvement of insulin sensitivity that occurs with weight loss (*e.g.*, the result of diet, illness, physical training) also accompanies bariatric surgery. However, there is evidence to support specific effects of surgery on insulin clearance, hepatic glucose production, and islet function. Understanding the mechanisms by which surgery affects these parameters of glucose regulation has the potential to identify new targets for therapeutic discovery. Studies to distinguish among bariatric surgeries on key parameters of glucose metabolism are limited but would be of considerable value to assist clinicians in selecting specific procedures and investigators in delineating the resulting physiology. This review is based on literature related to factors governing glucose metabolism and insulin secretion after the commonly used RYGB and VSG, and the less frequently used BPD and adjustable gastric banding. ***(Endocrine Reviews 40: 1394 – 1423, 2019)***

This review seeks to synthesize available data regarding the effect of bariatric surgery–improved glucose control, as well as the role for surgery to enhance islet function and insulin secretion. The sources cited for this review were selected from among the enormous body of research on this topic based on the author's view of their relevance and did not conform to a predefined search strategy. Although an attempt is made to emphasize the role of the islet β-cell, current data are often not sufficient to distinguish effects of insulin secretion from other mechanisms affecting glucose regulation. A general description of RYGB, VSG, BPD, or AGB, the principal procedures now used in clinical practice, is provided to assist the reader in interpretation of physiologic data, but the nuances of surgical technique and modifications of these and other procedures are outside the scope of this paper. Although there are few direct comparisons among this group of four surgical procedures, some inferences from the correlation of anatomy to physiology are made to raise questions and hypotheses. Data from human studies are emphasized, but a succinct description of preclinical research is included.

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Overview

Bariatric surgery in the age of the diabetes epidemic

The US rate of overweight/obesity was ~17% in 1976, grew to ~38% in 2010, and, if current trends hold, is projected to reach upwards of 75% by 2050 (1). The prevalence of diabetes in the United States was 2.5% in 1975 (2), rose to 14% in 2014, and is projected to crest >20% by 2050 (3–5). Although there are many etiologic factors for diabetes, it seems clear that increasing rates of overweight and obesity are a major

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ESSENTIAL POINTS

- Current bariatric procedures such as Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG), biliopancreatic diversion (BPD), and adjustable gastric band (AGB) modify the gastrointestinal tract in distinct ways, but all approaches improve type 2 diabetes mellitus (T2DM) in most patients
- Reduction of hyperglycemia following surgery is superior to medical treatment and/or caloric restriction; many patients with diabetes achieve remission after surgery, but this effect wanes over time with a gradual return of diabetes in some patients
- There is evidence for weight independent improvement in glucose control after RYGB, VSG, and BPD, which increase as weight-loss progresses; AGB improves diabetes in proportion to weight loss, similar to dietary restriction, with smaller effects than the other procedures
- The effects of surgery to improve insulin secretion are readily apparent in patients with T2DM but can also be detected in nondiabetic persons when insulin sensitivity is accounted for
- Stimulation of islet β-cells by enteral signals is increased after bariatric surgery; postprandial glucagon-like peptide 1 secretion is increased after RYGB or VSG and enhances insulin secretion
- Preclinical data using mouse genetic models to determine mechanisms of surgery to improve glucose metabolism have not yet identified definitive factors or pathways; in total, this work suggests that the physiologic response to surgery is complex and multifactorial

contributor to the epidemic rise in prevalence that has occurred during the past four decades. The estimated cost of treating obesity and diabetes in the United States rose from $212 billion in 2005 to $327 billion in 2017 (3), and it will invariably grow further given that adverse medical outcomes and health care costs increase exponentially with body mass index (BMI) (6). These costs are driven in great part by the fact that obesity and diabetes are largely incurable at present and must be managed as chronic diseases in most patients.

Multiple randomized clinical trials demonstrate that intensive dietary, behavioral, and/or exercise interventions result in ≤15% of patients with obesity achieving and maintaining long-term body weight goals (7). Similarly, intensive medical and behavioral measures lead to only a small minority of patients with type 2 diabetes mellitus (T2DM) reaching and holding glycated Hb (HbA_{1c}) targets (8–12). In contrast, there are now several clinical trials demonstrating that, depending on surgical intervention and postoperative time course, between 25% and 95% of patients receiving bariatric surgery achieve substantial, long-term body weight reduction (8–11). Moreover, improvement in glucose control among patients with diabetes having surgery is almost uniform, with nearly half maintaining nondiabetic glycated Hb (HbA_{1c}) without requiring diabetes medications. Notably, there has been an accumulation of evidence that some of the improvements in glucose regulation occur soon after surgery and are independent of weight loss. Bariatric procedures also have positive outcomes on hyperlipidemia, hypertension, and sleep apnea (13), addressing many of the major comorbidities that contribute to early death in patients with diabetes.

Historic development of bariatric procedures

The detailed history of surgical intervention for weight loss has been reviewed elsewhere (14, 15), but it is worth noting the progression of thought regarding the effects of bariatric interventions on glucose homeostasis. Although surgical interventions have been used to treat obesity since the 10th century (16, 17), the true precursors to modern bariatric surgery were actually developed to treat peptic ulcer disease and gastric cancer (18, 19). The weight-reducing effects of these interventions became clear as early as the 1940s, with reports that ~90% of patients experienced significant weight reduction, an observation initially attributed to diarrhea or loss of appetite (20). Although the focus in gastric surgery remained the treatment of peptic ulcer disease through the 1960s and 1970s (21), this period also saw some of the initial steps toward procedures developed specifically for weight loss. The advent of effective medical treatment of peptic ulcers in the late 1970s completely changed the clinical paradigm for treating this condition, at roughly the same time the average BMI of the American population began an exponential rise (22–24). These two events focused the attention of surgeons and other physicians on the treatment of obesity and comorbid conditions coincident with the development of several effective bariatric procedures. The growth in bariatric surgery as a therapeutic modality and topic for clinical research started in the 1980s, with greater attention on the development of new procedures, refined operative techniques, and more comprehensive outcome assessment.

Explanations for changes in glucose regulation following gastrointestinal surgery

Although the effects of gastrointestinal (GI) surgery on weight loss were the primary goal in developing bariatric surgery, the extraordinary effects these procedures have on glucose regulation can be gleaned even from early literature. Preclinical physiology laid the groundwork for understanding the potential for intestinal resection, or bypass, to reduce nutrient absorption and cause weight loss (25). Multiple case reports indicate that jejunoileal bypass improved glucose tolerance in conjunction with massive weight loss (26, 27). For example, it was noted that intestinal bypass reduced glucose excursion during an oral glucose tolerance test (OGTT) in the immediate postoperative time frame, prior to weight loss, a finding the authors attributed to poor glucose absorption (28). The role of the reservoir function of the stomach in glycemic regulation was noted in papers from the 1950s (29) and 1960s (30), with the potential for gastrectomy to improve diabetes noted by two groups (28, 31). The usual explanation for these findings was that gastrectomy, unlike jejunoileal bypass, accelerated nutrient absorption due to the lack of gastric capacity for temporary nutrient storage, precipitating acute enterally-driven hyperglycemia that caused high rates of insulin secretion (28, 32, 33). The simplicity of this model was questioned because absolute levels of glycemia or insulinemia were not always predictive of lower blood glucose (28), but work during this period established rapid gastric emptying after surgery as having a significant influence on glucose homeostasis. These studies were also foundational in defining the incretin effect, that is, the greater insulin secretion following oral compared with parenteral glucose (20, 34). Despite demonstrations that gastric resection and intestinal bypass modified glucose metabolism in patients, the lack of procedural uniformity, the morbidity of the patients treated with surgery, and the wide use of vagotomy, with its myriad effects on GI function, confounded the interpretation of the glycemic effects of early bariatric surgical procedures (35, 36).

With an increased focus on using GI surgery for weight loss, surgical methodology was refined through the 1980s and 1990s. In this setting the often-dramatic shifts in glucose homeostasis in the early postoperative course became more apparent and compelled the search for mechanisms by which this occurred. Concurrent advances in understanding insulin action, with the widespread use of glucose clamps in clinical research and advances in molecular understanding of the insulin signaling pathway in laboratory science, led to the observation that large-scale weight loss after surgery increased insulin sensitivity (7, 37). This observation fit with the then popular notion that T2DM was primarily a disease of insulin resistance (38), and it provided a model for the emerging benefits of weight loss surgery on diabetes.

Just as insulin resistance was demonstrated to be only a part of the pathophysiologic mechanism underlying T2DM (39), the notion that reduced insulin resistance after bariatric surgery explained all the changes in glucose metabolism was also challenged. The "rediscovery" of the incretin effect in the 1990s, as well as evidence that Roux-en-Y gastric bypass (RYGB) was associated with increased insulinotropic hormone secretion (40, 41), a finding initially reported many decades earlier (20), changed the consensus view of how bariatric surgery affected glucose metabolism. New findings suggested that bariatric procedures had broader effects on metabolic regulation through the stimulation of intestinal hormones that enhanced insulin secretion; the benefits of surgery to improve diabetes was reconceptualized to include an endocrine component that paralleled the use of incretin-based drugs in patient care (42).

The last decade has seen a profusion of human studies characterizing aspects of metabolic physiology after bariatric surgery that have identified other potential mechanisms that contribute to the changes in glycemia. Insulin secretion is generally improved, and this may occur independent of the incretin effect in T2DM patients, whereas effects in nondiabetic persons are subtler. Increased insulin clearance is one of the more proximate changes following RYGB that has been noted repeatedly, although how this is regulated and whether it is related to insulin secretion and insulin action are not yet known. Studies have increasingly focused on distinctions between hepatic and peripheral insulin sensitivity in explaining greater insulin action following surgery. However, despite considerable advances in experimental evidence and increasing sophistication in conceptual models, there remain major gaps in understanding the profound metabolic changes that follow surgical procedures.

Current implementation of bariatric procedures

Starting in the 1950s, surgery began to be conceptualized as a means to treat obesity and was put into practice by a small number of surgeons with special interest in the area. Most early procedures involved variations on intestinal bypass to promote some degree of enteral caloric wasting (43–46). These procedures were effective for weight loss and lowering circulating glucose and lipids (47), but over time they fell out of use due to a range of side effects that ranged from bothersome to morbid (36, 44, 48), as well as the increasing availability of safer, more effective procedures. The dawn of modern bariatric surgery can be traced to two influential papers by Mason. In the first, Mason and Ito (49) described the forerunner of the

current RYGB, and in the second, Mason (50) described a vertical gastroplasty that standardized gastric restrictive procedures and presaged the eventual development of vertical sleeve gastrectomy (VSG). Refinement of the RYGB and its broader application to weight loss in diabetic and nondiabetic subjects became more common in the 1980s, exemplified by the efforts of Pories and colleagues (40, 51, 52). This laid the groundwork for greater acceptance of bariatric surgery in the treatment of metabolic disease (13, 53). Scopinaro *et al.* (54–56) described biliopancreatic diversion (BPD) in 1976 as a safer version of jejunal bypass, and clinical development of this procedure proceeded in parallel to work on RYGB, albeit at fewer surgical centers. Subsequent advances that spurred development in the field include: the addition of a sleeve gastrectomy to the BPD, termed the duodenal switch (BPD-DS) (57); introduction of the adjustable gastric band (AGB) (58) as a refined gastric restrictive procedure for mechanically limiting meal size; application of laparoscopic methods to perform bariatric procedures (59), which heralded a steady decline in surgical complications; and the discovery that sleeve gastrectomy, as the first step in staged bypass procedures for the very obese, caused significant weight loss as a stand-alone surgery (60).

Schematic depictions of the major bariatric procedures currently in use are shown in Fig. 1 and described in detail elsewhere (61). The key anatomic features of the RYGB are the small gastric pouch emptying directly into the upper jejunum and the diversion of biliopancreatic secretions to the distal small intestine. With VSG a large percentage of the body of the stomach is removed, converting what is naturally a distensible muscular organ into a tight sleeve. Adjustable gastric banding is done by placement of an adjustable band on the proximal end of the stomach, restricting entry of food to a small pouch that empties slowly into the remainder of the stomach and eventually the small bowel. BPD, performed with or without a sleeve gastrectomy, shares some intestinal anatomy with RYGB but has significantly shorter alimentary and common limbs, and it has been demonstrated to limit caloric absorption (54). BPD is used only in a limited number of centers and comprises only a small percentage of bariatric procedures. All four of these procedures were initially thought to reduce food intake by physically restricting gastric volume, although this mechanism has been questioned in recent years (62–65).

The technical developments in surgery influenced a rise in the number of bariatric procedures performed in the United States to nearly half a million in 2013 (66), with RYGB and VSG being the two most common operations (>175,000 each in 2013); as of 2015, VSG had become the most common procedure performed in the United States (67). Refinements of RYGB and VSG have enhanced the speed and efficiency of surgery and reduced surgical morbidity dramatically (68). However, even with a greater number of procedures performed, and much more clinical investigation directed at their effects, many questions remain as to the physiologic basis of weight loss and other metabolic outcomes.

Effects of Modified GI Anatomy on Enteral Nutrient Flux

Gastric emptying

Current bariatric procedures all limit meal size. However, despite the anatomic dissimilarities between different surgical methods, the physiologic and clinical outcomes of surgeries that modify GI anatomy (*e.g.*, RYGB, VSG, and BPD-DS) are largely comparable. One common feature of these three surgical approaches is that of accelerated gastric emptying (69); this has been confirmed in each of these procedures using current state-of-the-art scintigraphic methods. There is general consensus in the literature that the rate of gastric pouch emptying in RYGB patients is increased by ~2.5-fold for liquids and ~3-fold for solids relative to nonoperated controls (70–75). Similarly, VSG increases the gastric emptying of liquid and solid nutrients by 2.5-fold and 2-fold, respectively (76–86). In contrast, although AGB restricts entry of nutrients from the gastric pouch above the band to the body of the stomach, passage through the pylorus to the intestine is not modified (87). It is likely that gastric restriction is the primary, and perhaps sole, mechanism by which AGB changes body weight (61). Despite the long clinical application of conventional BPD with a horizontal distal gastrectomy, the effects of this procedure on gastric emptying have not been as well studied as the other procedures. Rapid emptying has been attributed to the wide gastroenterostomy (88), but this effect may be mitigated to some extent by significantly reduced intestinal motility (89).

"AGB improves glycemia in patients with diabetes in a manner that parallels weight loss."

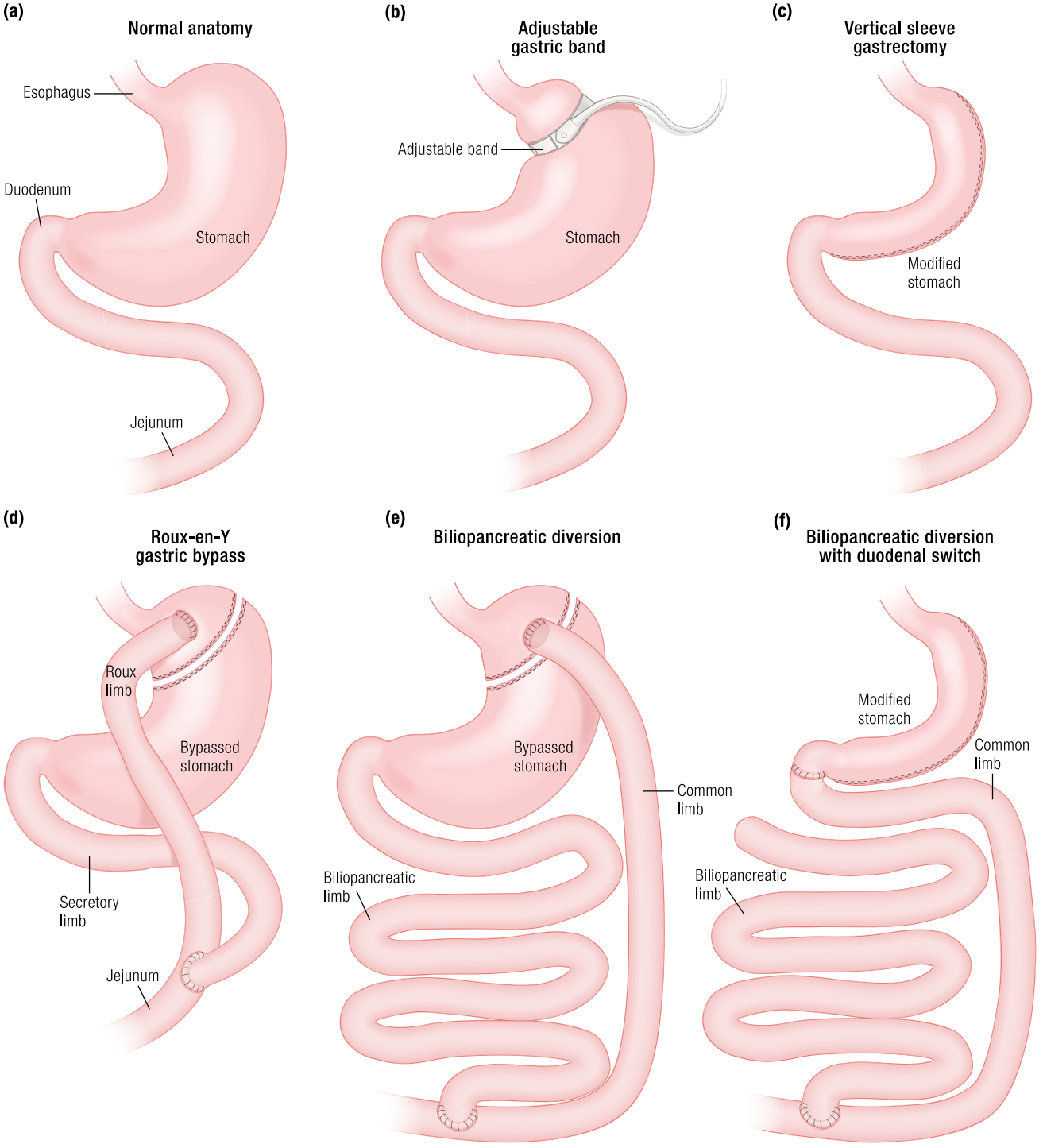
Nutrient absorption

Elevated gastric emptying rates after RYGB and VSG influence nutrient absorption. There is some variability in the absorption of different nutrient substrates, which has implications for islet regulation and insulin secretion after surgery.

Glucose

The antidiabetic effect of early bariatric surgeries was attributed to malabsorption of glucose (28); this is not true of most modern bariatric procedures. There is a distinctive pattern to glucose appearance and disposal following both RYGB and VSG, particularly early in the postoperative course. This entails a rapid, elevated peak in blood glucose followed by dramatic glucose clearance from the circulation (90–93). Although increased gastric emptying and alimentary motility can

Figure 1. Gastric and foregut anatomy of RYGB, VSG, AGB, and BPD. (a) Normal upper GI anatomy. (b) RYGB surgically transforms the stomach into a small pouch, then bypasses most of the stomach and duodenum by attaching the distal jejunum directly to the stomach. (c) VSG surgically removes most of the stomach, turning the gastric pouch into a tight sleeve. (d) AGB applies an adjustable band to the proximal portion of the stomach to restrict food entry. (e) BPD surgically modifies the stomach in a manner similar
to RYGB and connects the duodenum directly to the jejunum, bypassing most of the intestine. (f) BPD-DS includes surgical modification of the stomach much like a VSG coupled with the intestinal rerouting of a BPD.



decrease exposure to the absorptive brush border of the intestine in some GI disorders (94), there appear to be specific adaptations of the Roux limb (the upper jejunum connected to the gastric pouch) after RYGB that causes increased glucose absorption into circulation (77). This may involve increased expression of the glucose transporters GLUT2 and SGLT-1, as well as other glucose-sensing machinery, within the portion of the intestine exposed to nutrients (95–98). For example, SGLT-1 expression in the ileum is positively correlated with peak glucose concentration in one study (95). Research addressing the regulation of intestinal glucose transport after VSG is lacking, although glucose appearance after ingestion mimics that of RYGB (99). However, rigorous studies comparing nutrient absorption in VSG and RYGB could be very informative. For one thing, better understanding of carbohydrate digestion and absorption would contribute to the understanding of glucose tolerance. For another, the role of upper intestinal bypass on micronutrient and mineral absorption, for example, iron and calcium, would provide valuable clinical information for patient care.

Absorption of other nutrients

A number of malabsorptive pathologies accompany bariatric surgery. Iron deficiency after surgery is commonplace, occurring in nearly 40% of patients receiving RYGB (96, 100, 101), which is noteworthy given the role of iron in regulating islet function (102, 103). Modest fat malabsorption has been reported after RYGB (104, 105), with a decrease in the coefficient of fat absorption from ~90% to 70% per day (~10 to 12 g or <100 kcal) along with reduction of fat intake (104, 105). In fact, this degree of malabsorption has been proposed to contribute modestly to weight loss. There is also a reduction in cholesterol absorption and synthesis in patients with RYGB (106, 107).

BPD is frankly malabsorptive, with the shorter common limb for mixing nutrients with digestive factors contributing to ~50% reduced lipid absorption (54, 108). Interestingly, lower rates of cholesterol absorption after BPD are associated with increased rates of cholesterol synthesis (88). Absorptive capacity after BPD is reduced and seems to be fixed for lipid and energy substrates. Increased caloric consumption increases the degree of malabsorption, but not the amount of nutrient absorbed (109), with a 50-cm common limb maximal caloric absorption estimated to be ~1250 kcal (88).

In contrast to fat absorption, protein digestion and subsequent amino acid absorption seem to be elevated after RYGB surgery (74). This finding is somewhat counterintuitive given the diversion of pancreatic proteases to the distal small intestine, but it was the clear outcome of an experiment with robust methodology and is consistent with other studies of protein absorption after meals (110). This effect of RYGB on protein absorption stands in contrast to the 30% reduction of the coefficient for protein absorption with BPD (108). It is notable that glutamine, a stimulus for glucagon-like peptide 1 (GLP-1) secretion and a putative α-cell proliferation factor (111), displays increased absorption after surgery (112). These particular modifications to nutrient absorption after RYGB raise the possibility that changes in amino acid flux could influence islet function after surgery and contribute to glucose homeostasis.

The fixed absorptive capacity of the gut for energy absorption after BPD presumably involves starch (108), so that carbohydrate is also malabsorbed after this procedure, similar to fat and protein. Alternatively, there was no evidence of glucose malabsorption during an OGTT in a small group of subjects studied 1 month after BPD (113); this question needs formal study with more subjects for clarity. There have been few studies of intestinal function following VSG, but these would be useful in understanding the physiologic responses to this common procedure.

Effects of Bariatric Surgery on Glucose Metabolism

Effects on chronic glucose control in diabetes

AGB improves glycemia in patients with diabetes in a manner that parallels weight loss (114). Conversely, RYGB, VSG, and BPD have dramatic effects to reduce fasting glycemia and improve prandial glucose control almost immediately after surgery (115, 116). Whereas initial reports of surgical improvement in patients with diabetes were from observational studies (115–117), more recent randomized clinical trials have compared RYGB, VSG, and AGB to conventional treatments for diabetes. These studies have been essential for increasing the acceptance of bariatric surgery more widely among health care providers as a useful and appropriate treatment of the disease.

One of the remarkable features of bariatric surgery that has driven its use in treating diabetes is the apparent disease resolution in some patients. A meta-analysis of studies done through 2003 noted that soon after a bariatric procedure the great majority of patients achieved normal glycemic parameters without continued use of medication (13). These types of observations raised the possibility that surgery could permanently eliminate dysglycemia and its sequelae. However, observational studies of large postsurgery cohorts reported somewhat lower rates of 40% to 60% for disease remission (118) when using more formal criteria, that is, nondiabetic values for fasting glucose and HbA_{1c} without medication for 1 year (119). These rates of remission are comparable to longitudinal trials with VSG and RYGB. A number of investigators have developed models to predict which patients with diabetes are likely to have remission following surgery

based on different variables that include age, weight, and duration/severity of diabetes (120–122). More recently, the focus on remission as the primary criteria for assessing surgical effects on diabetes has been questioned because there is substantial improvement in glycemic control, and often reduction or cessation of diabetes medication use, even in patients who do not achieve criteria for remission (123). Thus, the focus on an optimal outcome may actually understate a more general benefit of surgery on diabetes. Moreover, patients with RYGB and VSG have distinct glycemic patterns with higher peaks and lower nadirs that may have an impact on glycemic exposure of tissues. These distinct responses have raised questions as to the applicability of conventional measures of average glycemia and diabetes control to bariatric surgery patients (124–126).

As longer systematic follow-up of bariatric cohorts has become more common, it is apparent that some patients who initially remit have a later return of diabetic hyperglycemia. Data from observational studies (127), retrospective database analyses (128), and randomized clinical trials (129) document relapses of diabetes after surgically-induced remission with a broad range of estimates from 3% to 30% over 5 years. Thus, there is now general agreement that long-term remission does not occur in all patients. The broad question raised by these observations is whether diabetes relapse is due to the steady and inherent progression of T2DM that has been confounding medical management for years (130), to factors specific to individual patients, or to mechanisms specific to a given surgical procedure. To date there are no validated predictors of diabetes relapse following a period of surgically-induced remission.

Longitudinal, observational studies suggest that bariatric surgery reduces the incidence of vascular complications (131), findings consistent with a recent meta-analysis (132). These findings are supported by analysis of a large patient database that noted fewer microvascular complications among patients with diabetes who had remission following bariatric surgery, mostly RYGB (133). In this analysis the length of time in remission was proportional to the reduction in rates of retinopathy, nephropathy, and neuropathy. However, in a retrospective analysis such as this (133), it is not possible to attribute reduced complications to remission *per se*; the results could also be explained by reduction of cumulative hyperglycemic exposure, the model for microvascular disease derived from medical intervention trials such as the Diabetes Chronic Complications Trial and the United Kingdom Prospective Diabetes Study. The attention focused on diabetes remission and relapse has been valuable for framing the impact of bariatric surgery on glucose metabolism. However, the critical question that remains only partially addressed is how effects of surgery on glucose metabolism translate into reduction of microvascular and macrovascular outcomes, and ultimately mortality related to diabetes.

Clinical trials

The observed therapeutic potential of bariatric surgery on diabetes outcomes (115, 116) set the stage for a rigorous test of this effect. A major hurdle was creating research infrastructure and recruitment strategies for randomization of patients with obesity to either conventional or surgical interventions. However, during the past 10 years a number of clinical trials designed to compare the effects of bariatric surgery with standard medical management on diabetes control have been completed and reported. These have included tests of all four common surgical procedures.

Adjustable gastric band. The first randomized clinical trial (RCT) of bariatric surgery directed specifically at treatment of diabetes used AGB as the surgical procedure (114). In this trial 60 subjects with obesity with T2DM were randomized to AGB or a medical/lifestyle strategy that emphasized caloric restriction and exercise and were followed for 2 years. During that period subjects given AGB had a mean 20% decrease in body weight compared with 1.4% in the lifestyle group. Rates of diabetes remission were significantly greater with surgery (73%) than with medical/lifestyle intervention (13%), and the amount of weight loss predicted nearly 50% of the variance in remission rate. Subsequently, two other RCTs have been reported that measured effects of AGB against nonsurgical management (134, 135). The first of these compared 22 subjects with AGB with 23 subjects following a lifestyle program for 1 year (134). Weight loss averaged 17% of starting weight in the AGB group, and 50% had partial or complete remission of diabetes (119). In contrast, subjects participating in the intensive lifestyle management program had 10% weight loss and none had diabetes remission. The final trial compared 18 subjects with diabetes with AGB to 22 subjects in a comprehensive weight management program for 1 year. In this trial the subjects treated with surgery lost 13% of starting body weight and the lifestyle management group lost ~9%; diabetes remission was comparable in the two groups, 33% for surgery and 23% for lifestyle.

Although the RCTs of AGB vs nonsurgical management for diabetes are all of relatively small size and differ in patient characteristics, specifics of lifestyle intervention, and duration, they do suggest several conclusions. First, T2DM is amenable to remission with significant weight loss, and more weight loss leads to greater effects. Second, AGB causes more weight loss than intensive lifestyle management programs, even those that include expert counseling on diet, exercise, behavioral programs, and medication management. Thus, even the least efficacious weight loss surgery has superior efficacy to nonsurgical approaches for glycemic control in patients with diabetes.

However, AGB does not appear to elicit major effects on glucose homeostasis beyond those explained by weight reduction.

Roux-en-Y gastric bypass. The Surgical Treatments and Medication Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial is the landmark study of bariatric surgery and diabetes (8, 136). This trial randomized 150 patients with obesity with poorly controlled T2DM to RYGB, VSG, or intensive medical/lifestyle management. The study had high rates of completion, extended follow-up (129), and a number of novel and important findings that have shifted the view of bariatric surgery as a clinical intervention. In this trial the medically treated group lost >5 kg in the first year with a decrease of HbA_{1c} from 8.9% to 7.5%, outcomes that would be considered above average for the standard management of T2DM. However, the RYGB and VSG groups lost 29 and 25 kg, respectively. Furthermore, ~40% of both surgical groups met the primary outcome of an HbA_{1c} ≤6%, significantly surpassing the 12% of medically treated patients achieving this target. These results demonstrated in dramatic fashion the powerful effects of surgery on diabetes control, with surgically treated subjects having reductions in HbA_{1c} of ~3%. After 5 years, 90% of the original cohort was retained in the study. The medically treated group maintained their mean 5-kg weight loss, but glucose control worsened over time, with the group mean HbA_{1c} rising to 8.5%. The RYGB group had modest weight regain (~6 kg) and an increase of the mean HbA_{1c} from 6.4 at 1 year to 7.4 at 5 years; for patients given VSG, the changes were ~7-kg weight regain and an increase in HbA_{1c} from 6.6% to 7.4%. Nonetheless, nearly one fourth of the surgically treated patients continued to meet the primary endpoint of a nondiabetic HbA_{1c} after 5 year. STAMPEDE demonstrated the large difference in effect size of surgery compared with top-rate medical management, and somewhat surprisingly the only slightly less powerful effect of VSG compared with RYGB. Moreover, the excellent rates of retention in the trial allowed the clear detection of glycemic worsening in all three study arms; these results are compatible with underlying progression of T2DM even in patients with a generally good response to surgery, although the average effects among the groups blur intersubject variability.

Other trials including RYGB have mostly confirmed the results of the STAMPEDE trial (10, 134, 137). For example, Ikramuddin *et al.* (10) reported that 6 years after RYGB there was a modest weight regain from the 1-year postoperative nadir of ~25% of baseline weight, and an increase in HbA_{1c} from ~6.2% 1 year after surgery to 7%. However, the rate of diabetes progression was about twofold higher in a group of subjects randomized to medical treatment during the course of the trial. In sum, there is strong evidence for potent effects of RYGB to improve glycemic control well beyond what conventional clinical measures can achieve. Although this effect is generally proportional to the amount of weight lost, an observational study of glucose lowering that compared AGB and RYGB suggests that the degree of diabetes resolution per pound of weight lost is greater with bypass (138), a view that is widely shared although not yet definitively established. Despite the magnitude of the surgical effect on HbA_{1c} and other measures of glycemic control, it is apparent that diabetes progresses in some surgical patients although it is not clear whether this is a general phenomenon (128).

Vertical sleeve gastrectomy. The results from the STAMPEDE trial established VSG as significantly more effective for treating hyperglycemia than medical management alone (129). Moreover, subjects with VSG had only modestly less weight loss and rates of diabetes remission than those with RYGB. These findings are supported by the results of two trials comparing the efficacy of RYGB and VSG in subjects with obesity for 5 years (139, 140). One of these studies, SLEEVEPASS, a randomized trial comparing RYGB or VSG, included a substantial number (~40%) of subjects with T2DM. Weight loss at 1 year was comparable between the surgeries, and diabetes resolved or improved in 84% of the subjects with VSG and 93% of the RYGB group (141). After 5 years, weight loss was generally maintained, and HbA_{1c} reduction was similar with the two surgeries (~6.6%) despite the RYBG group having ~14% greater body weight loss (140). Similar results were reported in the SM-BOSS trial (139), with comparable, although slightly greater, weight loss in RYGB compared with VSG that was maintained for 5 years. At this last follow-up time point, >60% of the subjects had remission of diabetes with mean HbA_{1c} of 6.2% in the VSG group and 5.9% in the RYGB subjects. Overall, VSG has effects on body weight and glycemic control that compare with RYGB; although not a universal finding, there is a trend in these comparisons for VSG to be slightly less effective.

"Overall, VSG has effects on body weight and glucose control that compare with RYGB..."

Biliopancreatic diversion. Previous retrospective analyses (142, 143) and a systematic review (144) report greater amounts of weight loss and diabetes resolution in patients with BPD compared with those with RYGB, albeit with greater adverse surgical effects. BPD has been compared with medical treatment of diabetes outcomes in a small randomized controlled trial that compared effectiveness to medical management (11, 145). In this study, 60 patients with obesity with T2DM were randomized to medical/lifestyle treatment, BPD, or RYGB; the different operations were performed by separate surgical teams. At 2 years, 19 of the 20 subjects given BPD, 15 of 20 with RYGB, and none of the medically treated group reached the primary outcome of diabetes remission (fasting glucose <100 mg/dL and HbA1c <6.5% with use of no glucose-lowering medications). The medical/

lifestyle-treated subjects lost ~5% of starting body weight, whereas the surgical groups both lost ~33%. The subjects with diabetes started this trial with HbA_{1c} values of 8.6% and reached values of 8.3%, 6.3%, and 4.9% in the medical, RYGB, and BPD groups, respectively, at 2 years. When examined 5 years after surgery, 7 of the 19 RYGB patients and 12 of 19 BPD patients maintained diabetes remission, and the BPD group had lower mean HbA_{1c}; the medically treated group had no diabetes remission. Notably there was not a clear correlation of diabetes remission with amount of weight loss. A second trial compared 60 patients randomized to RYGB or BPD-DS and followed for 5 years; only a small number of patients in this cohort (≤20% in each group) had diabetes before surgery (146). The BPD group had greater weight loss at the 5-year follow-up, and mean fasting glucose and HbA_{1c} were lower than in the RYGB group. However, both groups had similar diabetes remission rates.

The results of these prospective studies with BPD are compatible with those of trials with RYGB and VSG in demonstrating the significant difference in diabetes improvement with surgery compared with medical management. Although there is general belief that the effects of BPD on weight loss and diabetes improvement are greater than other procedures, larger randomized comparisons are needed to validate the results of observational studies on potential differences in beneficial and adverse effects among procedures.

Mechanisms by which surgery affects glucose metabolism

The superior efficacy of bariatric surgeries to lower blood glucose compared with conventional medical or lifestyle interventions has spurred numerous studies to determine the mechanisms involved. What has been particularly compelling is the rapidity of this response. In a study of 31 patients with T2DM, blood glucose was reduced ~2 mM 6 days after RYGB, coincident with an ~60% decrease in fasting insulin (147). A more recent study including 18 women with diabetes undergoing RYGB reported an ~20% decrease in fasting glucose within 3 days of surgery (148). These findings are in keeping with clinical impressions that many patients with diabetes who required medical management before undergoing RYGB do not need treatment of hyperglycemia in their postoperative hospital course (115, 116). Two points that have been debated as explanations for the rapid glucose lowering after surgery are: (i) the effect of caloric restriction *per se*, independent of anatomic changes to the gut to mediate this effect; and (ii) whether amelioration of insulin resistance is central to the response.

Role of caloric restriction

There is evidence that dietary caloric restriction for as little as 1 week can improve insulin action and insulin secretion (149, 150). In these studies, low calorie intake was associated with 2 to 3 kg of weight loss and significant reduction in fasting glucose. Thus, a number of studies have compared the effects of a very low-calorie diet (VLCD) to RYGB, during periods of 1 to 3 weeks, to determine the effects of decreased food intake on parameters of glucose metabolism. The study designs used in these experiments were either parallel assessments of diet- and surgery-treated subjects (151–155) or within-subjects comparisons of patients given VLCD before surgery and standard treatment after RYGB (156–159). Most of these studies were small, with ~10 subjects per group, and the discrepant results may be due to their modest statistical power to distinguish differences between interventions. For example, studies using either parallel or within-subjects comparisons noted similar reductions in fasting glucose and insulin with either RYGB or VLCD and concluded that caloric restriction after surgery accounts for the rapid reduction of blood glucose in subjects with diabetes (152, 157, 160); a similar result was reported for subjects with diabetes studied 3 days after BPD (161). Alternatively, a study using both experimental approaches reported significant reductions in fasting glucose among subjects with diabetes with RYGB compared with those receiving a VLCD (156). A recent paper reported results from 20 nondiabetic subjects with obesity assessed before and 1 week after a 600 kcal/d diet, and again 3 months later, before and 1 week after RYGB (158). Following dietary restriction there was a 2-kg weight loss but no significant changes in fasting glucose and insulin, nor in fasting or insulin-stimulated glucose turnover. In 10 of these subjects who subsequently had RYGB there was a 5-kg weight loss, with weight-adjusted improvement in hepatic and peripheral insulin sensitivity. Although this study supports effects of RYGB on glucose metabolism independent of caloric intake, the small sample and normal glucose tolerance of the subjects limits extension to the salutary effects of surgery on diabetes.

Comparisons of dietary restriction with surgery on parameters of glucose metabolism are confounded by the known effects of surgical stress to cause insulin resistance (162–164). Thus, equivalent improvements in glucose regulation in unstressed subjects on VLCD, and those with recent RYGB, who have pain, inflammation, medication effects, and other factors impacting metabolism, must be considered carefully. This point is exemplified by the study of Lingvay *et al.* (157) in which patients treated sequentially with VLCD and RYGB had similar reductions in fasting glucose during 10 days, but with differing patterns. During the diet intervention, fasting glucose decreased steadily, whereas after surgery there was an increase in glycemia on the first postoperative day and relative hyperglycemia for the next 5 days before levels decreased below preoperative values. Indeed, it is not uncommon for endocrinologists to consult on patients

whose diabetes has worsened after abdominal surgery even with caloric restriction.

One means of controlling for postoperative stress while investigating the impact of caloric restriction after surgery is comparison of gastric-restrictive procedures such as AGB to RYGB before significant weight loss; the assumption here is that AGB strictly reduces food intake, whereas the more substantial changes to GI anatomy with RYGB elicits effects independent of energy balance. Korner *et al.* (165) reported similar reductions in fasting insulin and glucose in groups of nondiabetic subjects with obesity with ABG and RYGB 2 weeks after surgery. Similarly, Kashyap *et al.* (166) observed similar glucose lowering with banding and bypass at 1 week postoperative but noted a greater decrease in fasting insulin in the bypass group and inferred a greater improvement of insulin sensitivity. More recently, Gastaldelli *et al.* (158) compared fasting measures and the response to a euglycemic–hyperinsulinemic clamp among nondiabetic subjects 1 week after AGB or RYGB. In this study subjects lost ~5 kg of body weight with both procedures and had comparable, modest reductions in fasting glucose and insulin. Although endogenous glucose production was reduced and hepatic insulin sensitivity improved after both AGB and RYGB, only the subjects with bypass had improvements of peripheral insulin sensitivity, measured as either adipose tissue or skeletal muscle responses. The measure with the most convincing difference between the two surgery groups was insulin clearance, which was significantly increased after RYGB. This finding has been reported 1 week after RYGB by a second group (167), and the difference between band and bypass noted by a third (168). The results of the Gastaldelli *et al.* (158) study support differences in the physiology induced by RYGB and ABG, but similar to the other short-term comparisons of these procedures they have only marginal statistical power to identify definitive differences.

When taken together, studies comparing RYGB and either VLCD or ABG indicate that the rapid reduction in fasting glycemia, reflecting improved glucose regulation and the potential to stop antidiabetic medications (115, 116), is accounted for in great part by reduced caloric intake. However, there is evidence that RYGB has additional effects beyond acute energy balance on insulin clearance and insulin sensitivity. Determining the nature and impact of these changes will require a directed and amply powered study.

Effects of bariatric surgery on insulin sensitivity

The improvement of insulin sensitivity in the early postoperative course has been studied in a series of small but rigorous studies, focused mostly on patients with RYGB. These studies have measured hepatic glucose production (HGP) using isotope dilution methods and used euglycemic–hyperinsulinemic glucose clamps to determine insulin sensitivity; at present, these are the most accurate and precise techniques available for studies of small and medium size, for example, 20 to 50 subjects. One week following RYGB, Bojsen-Møller *et al.* (169) noted reduced fasting HGP, a trend toward greater suppression of HGP by insulin, and no change in peripheral insulin sensitivity. Similar results were published by Gastaldelli *et al.* (158) in 10 nondiabetic subjects 1 week after RYGB, including a significant reduction of fasting HGP, a threefold suppression of HGP with insulin that did not reach statistical significance, and no change in peripheral insulin sensitivity. Two studies involving small groups of subjects 2 weeks after RYGB (170, 171) reported comparable findings: significant reductions in fasting insulin and glucose, reduced basal HGP, and no effect on hepatic or peripheral insulin sensitivity. By 1 month after surgery HGP is more robustly suppressed during an insulin clamp in both subjects with diabetes and nondiabetic subjects compared with their preoperative state (172). Some groups also report a small improvement of peripheral insulin sensitivity at this time (173, 174), whereas others see no change (172, 175). Taken together, these data, obtained with the currently accepted best analytic methods, do not provide a definitive explanation for immediate/early changes in glucose metabolism after surgery. The most consistent and significant observation is a large decrease in basal insulin concentrations. There seems to be a tendency for HGP to be reduced in the early period following surgery, yet it is unclear whether this is a function of insulin sensitivity or some other regulatory input. Peripheral insulin sensitivity seems to lag behind hepatic changes, with improved glucose disposal starting to become apparent only 4 weeks postoperatively.

Multiple studies have reported that insulin resistance as determined by HOMA modeling of fasting insulin and glucose concentrations improves following RYGB (176–178), VSG (179–181), and AGB (182). HOMA modeling to derive an index of insulin sensitivity (HOMA-S) (183) has been the most common assessment of changes in glucose metabolism used in studies of bariatric surgery because of its simplicity. HOMA-S requires only fasting values of insulin and glucose, and it is thought to reflect primarily hepatic insulin sensitivity, although in recent iterations the model also accounts for peripheral insulin action (183). This approach has been used to support the view that the acute effects of surgery on glycemia are due to rapid improvement of insulin resistance in the liver. Importantly, however, note that the application of HOMA in surgical subjects has been challenged in studies that also use hyperinsulinemic glucose clamps to measure insulin action (163, 175, 184). Although HOMA-S measures generally correlate with estimates of insulin sensitivity derived from clamp studies, there

"There is evidence that RYGB has additional effects beyond acute energy balance on insulin clearance and insulin sensitivity."

are differences in precision, a problem that is magnified in studies with small sample sizes (183). Moreover, because insulin secretion is pulsatile, proper application of HOMA modeling should use three fasting blood samples taken at 5-minute intervals to determine plasma insulin and glucose concentrations (183). This protocol recommendation has not been followed, or not been noted, in many studies of bariatric surgical subjects, and use of single measures of insulin for HOMA computations reduces the accuracy of the measure, another problem that can affect studies with relatively small sample sizes.

A major potential confounder of HOMA-derived insulin sensitivity measures in studies of RYGB subjects is the rapid and significant enhancement of hepatic insulin clearance that occurs in the first postoperative week (150). An early increase in hepatic insulin clearance has been noted for RYGB, VSG, and BPD in both subjects with diabetes and nondiabetic patients (167, 185, 186). This causes fasting insulin levels to decrease by 25% to 50% (158, 169, 174, 187) and significantly affects estimates of insulin sensitivity from models that use plasma insulin as a divisor; this includes the HOMA-S, QUICKI, and Matsuda models, and even indices using tracer-derived measures of HGP (158, 169). It is not clear how these early changes in hepatic insulin clearance after surgery are related to insulin sensitivity. Although it has been proposed that hepatic insulin clearance is roughly equivalent to hepatic insulin sensitivity (174), this has not been proven experimentally. In fact, whereas changes in hepatic insulin sensitivity in the week after RYGB are equivocal when measured by direct methods (*i.e.*, euglycemic insulin clamps with isotopic dilution), estimates based on HOMA almost uniformly demonstrate large effects. Recent work in an animal model suggests that hepatic insulin clearance is related to peripheral, but not hepatic, insulin sensitivity, although this relationship has not been extended to humans (188). What is needed are direct, independent measures of hepatic insulin clearance and action to determine whether changes in these parameters after surgery are related or coincidental. Until a relationship between hepatic insulin clearance and insulin sensitivity in postoperative humans is established, the assumption that HOMA is a reliable reflection of hepatic insulin sensitivity should be made with caution (184).

It is now very clearly established that in both subjects with diabetes and nondiabetic subjects who have substantial (*e.g.*, >15%) weight loss following surgery, hepatic and peripheral insulin sensitivity improves significantly (152, 169, 180, 189, 190). Although the rate of weight loss is faster, and generally greater in absolute terms, for RYGB, BPD, and VSG than for ABG (189, 191–194), resolution of insulin resistance is predictable past a general threshold of reduced body weight. This is evident in longitudinal studies assessing the temporal pattern of insulin sensitivity after surgery. For example, when insulin action has been measured using glucose clamps in RYGB subjects studied in the first month after their operation, results have been disparate (158, 169, 174, 184). However, by 3 months there is generally a large reduction in insulin resistance that persists for a year or more (99, 169, 170, 195, 196); similar longitudinal results have been described for BPD (197). Improved insulin sensitivity after weight loss is detectable in both skeletal muscle and adipose tissue and is associated with changes in molecular mediators of insulin action (198, 199). Once successful weight loss becomes stabilized, insulin sensitivity is proportional to body weight when measured using glucose clamps (99, 185, 189, 200). However, when estimated using a formula based on fasting insulin (*e.g.*, HOMA), the relationship of insulin sensitivity to body weight is lost (197, 198), possibly because increased insulin clearance after RYGB is not related to BMI.

There are two studies that have reported the course of insulin sensitivity following BPD using glucose clamps. In a study by Guidone *et al.* (201), 10 subjects with obesity with T2DM had resolution of hyperglycemia 1 week after BPD that was associated with a doubling of insulin sensitivity; glucose tracers were not used to differentiate hepatic and peripheral insulin action. Insulin sensitivity did not change further at 4 weeks, and there was a proportional decrease in fasting insulin secretion. Astiarraga *et al.* (202) reported compatible findings, with a significant improvement of insulin sensitivity 2 months following BPD in patients with T2DM. In this study, fasting and insulin suppression of HGP were lower at 2 months than before surgery. This is a limited set of evidence on which to make firm conclusions, but these findings of more rapid improvement of insulin sensitivity with BPD are in keeping with the notion that this procedure has a greater impact on metabolic physiology than do other surgeries.

It is notable that several studies have reported that subjects with diabetes and nondiabetic subjects receiving bariatric surgery are actually more insulin sensitive than are weight-matched subjects without surgery (170, 198). This observation has not been pursued with more comprehensive studies, for example, of body composition and tissue-specific insulin action, but it raises the possibility that surgery has an impact on insulin action that is out of proportion to the effects on weight loss. Finally and importantly, note that weight loss and improved insulin sensitivity do not predict diabetes remission across all patient populations (203, 204); in fact, improved glucose control has been described to be largely independent of improved insulin sensitivity (91, 205).

Effects of surgery on postprandial glycemia

Although postprandial glycemic profiles in subjects with AGB are similar to controls (87, 206), both RYGB

and VSG have marked effects on postprandial glucose excursions. The more rapid delivery of carbohydrate to the absorptive surface of the intestine (207) leads to a sharp upward deflection of blood glucose that is higher than peak levels in subjects without GI surgery (189, 206). Despite the elevated peak glucose levels after either an OGTT or mixed meal tolerance test (MMTT) there is an improvement in glucose tolerance following RYGB and VSG as reflected in a reduction in the area under the curve for glucose during the meal (176, 208–210). This prandial profile demonstrates both the accelerated meal glucose appearance in VSG and RYGB (185, 209), but also the superior clearance of glucose conferred by surgery. In fact, it is common for RYGB patients, and also for those with VSG, to have glucose nadirs during test meals that are significantly lower than their fasting levels (185). This exaggerated pattern of glucose dynamics reflects both the impact of altered GI anatomy as well as adaptive changes that allow the homeostatic challenge of increased nutrient flux to be managed.

BPD performed with a distal gastrectomy does not cause the rapid rise in prandial glycemia typical of RYGB and VSG (113, 202), but formal measures of gastric emptying or meal glucose appearance were not performed in these studies. Of note, patients with BPD-DS studied several days after surgery had glycemic excursions following a mixed meal that were completely blunted, and much smaller than the excursion seen in a matched group of patients with sleeve gastrectomy despite similar gastropyloric reconstruction with the two operations (211). Although not formally measured, this result suggests impaired glucose absorption after BPD-DS. Despite, or perhaps because of, impaired absorption of glucose in the transposed ileum, GLP-1 levels in these early postsurgery subjects were substantially elevated. This effect of BPD on glucose absorption appears to wane over time, as prandial glycemia levels in patients with BPD-DS match those of patients with SG when studied at 3 months and 1 year postoperatively (212). These findings suggest the interesting possibility that there is adaptation in the alimentary limb of patients with BPD over time that enhances carbohydrate digestion and uptake (211).

Effects of bariatric surgery on insulin secretion

Although procedures such as VSG, RYGB, and BPD have a number of reported effects on islet function, there remains some uncertainty as to what the proximate actions of surgery on insulin secretion are, and whether all procedures have similar effects. However, what is clear is that postsurgical patients with T2DM show more immediate and definite improvements of insulin secretion as measured by a number of methodological approaches than do those without antecedent diabetes (173, 213, 214). This difference in response raises the possibility that bariatric procedures induce specific responses to rectify abnormalities in β-cell function, a tractable but as yet unsubstantiated hypothesis. Regardless, the current state of literature in this area suggests that postsurgical effects on insulin secretion are more readily understood by considering the responses of subjects with diabetes and nondiabetic subjects separately.

Nondiabetic subjects. Insulin secretion predictably mirrors the glucose excursion during either an OGTT or MMTT following RYGB, VSG, and BPD. Studies of subjects with VSG and RYGB are consistent with meal stimulation engaging a variety of factors that drive hyperinsulinemia, starting with steeper glycemic excursions (90, 206, 215–217), and including greater stimulation from enteral factors such as incretins (218). Therefore, the early β-cell response to meals is predictably increased following either RYGB or VSG, with an excursion that peaks and returns to baseline more rapidly than the profile of subjects without surgery. In contrast, the pattern of prandial insulin secretion in persons with BPD, with or without the DS, is not as dynamic as described in those with VSG or RYGB (113, 202, 212, 219). These findings support the importance of ambient glycemia, independent of other effects of surgery, in shaping the β-cell response to meals, and they indicate that differences of 2 to 4 mM in peak blood glucose concentrations have a major impact on the magnitude of secretion in nondiabetic persons (91, 189, 211). One challenge this has posed to assessing insulin secretion using meal stimuli is that the rapid dynamics of meal absorption, glycemia, and insulin responses among surgical patients adds a temporal factor to comparisons and can confound simple summaries of secretion (*e.g.*, area under the curve).

"...GLP-1 does not seem to account for the greater glucose tolerance among patients with diabetes after surgery."

Perhaps the most important consideration when evaluating the effects of bariatric surgery on insulin secretion is the impact of insulin sensitivity. Among nonsurgical patients there is an inverse relationship between measures of insulin secretion and insulin sensitivity that is generally interpreted as β-cell compensations to provide appropriate amounts of insulin to maintain glucose homeostasis (Fig. 2) (220). In both healthy subjects and subjects with diabetes this relationship has been described by a rectangular hyperbola such that the product of insulin secretion and insulin sensitivity are a constant, termed the disposition index (DI) (221). Application of the DI after bariatric surgery is exemplified by the study of Bradley *et al.* (189), which examined nondiabetic subjects before and after 20% weight loss with either AGB and RYGB. Insulin sensitivity measured by euglycemic glucose clamps increased 50% to 60%, and total insulin secretion rate (ISR) during a mixed meal decreased ~20%, with both surgeries. Thus, the DI was increased by nearly 75% in both groups and was taken as evidence of enhanced β-cell function that would not have

been identified were plasma insulin or C-peptide levels considered in isolation. Similar relationships have been described before and after VSG (91) and BPD (113) and emphasize the importance of interpreting insulin secretion in the context of insulin sensitivity. Importantly, however, note that the validation of the DI as a hyperbolic function of insulin secretion and sensitivity has only been done in nonsurgical subjects (221–223). It is plausible that surgery alters this relationship, and formal testing of the interaction of secretion and sensitivity after RYGB, VSG, or BPD would be an important addition to the knowledge base in this area.

A number of studies have used IV glucose as a stimuli to assess insulin secretion following RYGB, VSG, or BPD (173, 196, 214, 224–226). This approach removes the effects of rapid enteral nutrient flux on β-cell function and allows simpler comparisons between subjects before and after surgery, or with nonoperated controls. Additionally, the frequently sampled IV glucose tolerance test protocol can be used with the minimal model of glucose kinetics to estimate insulin secretion and sensitivity from the same data set (196, 226), an approach that minimizes day-to-day variability and adds greater precision to the connection between insulin secretion and action. These studies demonstrate minimal change (173), or even a reduction (196, 226), in the acute insulin response to glucose over time as postsurgical patients lose weight and reduce insulin resistance. However, when insulin secretion is corrected for insulin sensitivity as the DI, most studies report that β-cell responsiveness to glucose stimulation is improved in glucose-tolerant subjects with obesity after surgery (173, 196, 226). Similar to studies using oral challenges to glucose tolerance, the body of work using IV glucose tolerance tests supports improved glucose homeostasis following bariatric surgery as a function of both insulin secretion and insulin sensitivity. The question raised by studies examining insulin secretion in response to IV stimuli is how improved β-cell function is mediated, as improved responsiveness occurs in the absence of inputs from the gut and central nervous system and thus is independent of postsurgical anatomy. The data available at present are compatible with surgery causing adaptations intrinsic to the islet, a conclusion supported by recent findings in a preclinical model (93).

There is recently published evidence that some inherent capabilities for insulin secretion may be attenuated after surgery. Salehi *et al.* (227, 228) reported that subjects with RYGB for several years have reduced β-cell sensitivity to glucose and incretins. In these experiments, subjects were given graded infusions of glucose, glucose-dependent insulinotropic polypeptide (GIP), or GLP-1, and ISR compared with a group of weight-matched subjects without surgery. The RYGB subjects had almost uniformly lower insulin secretion in response to comparable glycemic or incretin

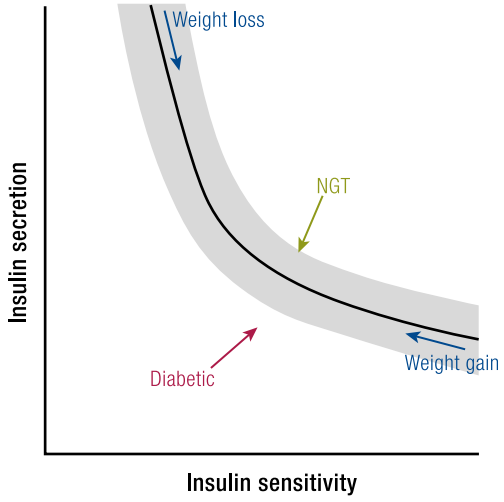


Figure 2. Model of changes in β-cell function following RYGB. An inverse relationship between insulin secretion and insulin sensitivity exists in surgical and nonsurgical patients. This empirically derived relationship is generally interpreted as β-cell function adapting to meet the demands of increasing insulin sensitivity (with weight loss) or increasing insulin resistance (with weight gain). Nondiabetic persons have decreased insulin secretion after RYGB, as β-cell function is blunted to account for greater insulin action. In contrast, subjects with diabetes have improvements in both insulin secretion and insulin sensitivity. See (213, 214).

stimulation that was not accounted for by differences in insulin sensitivity derived from a glucose clamp. These findings suggest that, at later time points following surgery, β-cell sensitivity is dampened to factors such as glucose and GLP-1 that circulate at high concentrations after meals, plausibly to prevent hypersecretion and hypoglycemia. Although these findings require confirmation, they do raise the possibility that β-cell function adapts over time after surgery to optimize or maintain glucose homeostasis.

Finally, assessment of insulin secretion in patients after VSG, RYGB, and BPD must account for the increase in hepatic insulin clearance that occurs soon after surgery (167, 185, 186). Using changes in plasma insulin alone can be misleading and mute the magnitude of insulin secretion (167). Accurate assessments of β-cell function require measurement of C-peptide, and it has become common to use deconvolution models to derive ISRs (113, 229), which provides a more precise estimation of β-cell function and allows accurate calculation of insulin clearance. However, deconvolution of C-peptide kinetics relies on estimates derived from nondiabetic subjects (230), a parameter that has not been generated for people with bariatric surgery. Although there is no reason to expect that surgery would alter C-peptide kinetics, this has not been directly tested.

Patients with diabetes. Although the effect of bariatric surgery on insulin secretion can be a subtle or contingent finding in nondiabetic subjects, the effect is

more obvious in persons with preoperative diabetes. A number of studies have reported restoration, if not normalization, of first phase insulin release (FPIR) to IV glucose in subjects with T2DM studied 1 to 4 weeks after RYGB or BPD (173, 214, 224, 225). This finding is notable for its consistency across a range of cohorts, the rapidity of the response (often before significant weight loss or change in insulin sensitivity), and because loss of FPIR is one of the hallmark β-cell lesions associated with diabetes (231). The association of rapidly corrected fasting hyperglycemia and enhanced FPIR supports a model in which β-cell adaptation contributes to diabetes resolution after procedures such as RYGB, VSG, and BPD.

Diabetic patients also have improved insulin responses to enteral challenges following RYGB, VSG, and BPD. Measures of insulin secretion in response to mixed nutrient meals (185, 213, 225, 232) or oral glucose (173, 180, 225, 233) are increased in the first month following common bariatric procedures; a single report comparing RYGB and AGB suggests that gastric restriction alone does not have this prompt action to increase insulin release (166). Improved insulin secretion in response to carbohydrate ingestion is maintained in subjects with diabetes even after substantial weight loss and reduced insulin resistance (169, 215, 232). This pattern of concurrent improvement of insulin secretion and insulin sensitivity differs from that of nondiabetic subjects after surgery in whom these parameters have an inverse relationship (196, 226), and it raises the possibility that bariatric surgical procedures have distinct actions on diabetic and nondiabetic β-cells (Fig. 2).

One exception to the pattern of increased insulin secretion and sensitivity after surgery was reported by Grenier-Larouche *et al.* (197) in a cohort of patients with mild T2DM (A_{1c} ~6.6%) who were followed for 12 months following BPD. These subjects had ISRs measured with graded IV infusions of glucose and related to insulin sensitivity measured with hyperinsulinemic clamps. There was no difference in ISR or DI 3 days after surgery compared with before surgery. However, by 3 months the subjects had mild, nonsignificant decreases in ISR with significant improvement in insulin sensitivity leading to a higher DI; this pattern was maintained at 12 months. Similar findings were reported in a group of subjects studied during 3 years after RYGB with oral and graded IV glucose tolerance tests (234). This group of 16 subjects with diabetes, who all had remission through the study, had measured ISR responses to oral glucose that were comparable with nondiabetic controls starting 1 month after surgery and extending for 3 years. However, there was much less improvement in IV glucose-stimulated insulin secretion. The findings suggest that although enhanced incretin action can normalize prandial insulin responses in subjects who were formerly diabetic, more subtle stimuli, such as graded glucose infusions, may be a more sensitive measure of the capacity inherent in β-cells.

The importance of β-cell function in the response of patients with diabetes to bariatric surgery is also reflected in the prediction of disease remission. Most prediction models incorporate some index of diabetes severity such as fasting or stimulated C-peptide. These measures have been shown repeatedly to be independent predictors of diabetes outcomes from surgery (235–238). Although C-peptide is included in some broader prediction models (239), that compromised β-cell function before bariatric surgery reflects the resolution of diabetes afterward speaks to the importance of improved insulin secretion to mediate surgical effects.

Hyperinsulinemic hypoglycemia syndrome. As more patients have had bariatric procedures during the past two to three decades, clinicians have started to recognize a syndrome of postprandial hypoglycemia, mostly in patients several years following RYGB. Originally attributed to the dumping syndrome that has long been observed in patients with gastric surgery (240), several case series described a more severe condition, often involving neuroglycopenic symptoms (241). Since these initial descriptions it has become clear that a subset of patients with RYGB develop recurrent hypoglycemia, with glucose levels <3 mM occurring 1 to 3 hours after meals. These hypoglycemic periods are characterized by hyperadrenergic and neuroglycopenic symptoms (242–244).

The prevalence of hyperinsulinemic hypoglycemia syndrome is not well established, in great part because of a lack of consensus on diagnostic criteria (245). Rates have been estimated at <1% based on hospitalization for hypoglycemia (246) or self-reporting (247), 13% based on a longitudinal cohort study (248), up to 30% based on an OGTT or MMTT (249, 250), and as high as 75%, mostly asymptomatic, based on continuous glucose monitoring (250, 251). Affected patients have hypoglycemia after some, but not all, meals (252), which may be accounted for by differences in amounts of carbohydrate ingested (253). Clinical hypoglycemia has been described rarely in patients with VSG (254), and almost never after AGB. A single case report of hypoglycemia after BPD-DS was associated with advanced liver disease (255).

Studies of subjects with the postsurgery hypoglycemia syndrome have consistently demonstrated relative meal-induced hyperinsulinemia compared with matched subjects with RYGB without a history of symptomatic low glucose (244, 254, 256, 257). This difference becomes magnified when plasma insulin is adjusted for prevailing glycemia (243). There is also a tendency for subjects with the most dramatic symptoms to have both higher rates of insulin secretion and lower rates of insulin clearance (186). The high rates of meal-induced insulin secretion in subjects with the hypoglycemia syndrome were initially attributed to

increased GLP-1 secretion and action (241, 243), but subsequent studies including greater numbers of subjects did not demonstrate significant differences in plasma GLP-1 (229). Moreover, the insulinotropic activity of meal-induced GLP-1 was not increased in RYGB subjects with hypoglycemia compared with a group of matched, asymptomatic RYGB individuals (229). However, blockade of the GLP-1 receptor (GLP-1R) with the peptide exendin-(9–39) almost completely mitigates meal-induced hypoglycemia in symptomatic RYGB subjects (217, 258). These studies implicate increased sensitivity to GLP-1 as a mechanism for the syndrome of hyperinsulinemic hypoglycemia in a subset of gastic bypass subjects, and they suggest a therapeutic strategy for their treatment.

Some post-RYGB patients have had recurrent hypoglycemia to such severity that partial or subtotal pancreatectomy was performed to blunt hypersecretion of insulin (242, 259, 260). Microscopic examination of surgical specimens from these patients were described as showing features of nesidioblastosis, with hyperplasia of islet β-cells and increased nuclear size, suggesting changes at the tissue level that could account for hypersecretion of insulin (242, 260–262). The possibility that islet cell growth after RYGB underlies clinical hypoglycemia is supported by the typical delay of 1 to 2 years before the onset of symptoms and by a handful of cases that describe recurrence of symptoms following partial but not total pancreatectomy [*e.g.*, (259)]. However, postsurgical β-cell hypertrophy has been questioned by other investigators who could not confirm the histologic picture of nesidioblastosis in a reexamination of some of these pancreatectomy samples (263). Furthermore, a general concern about the pathological investigation of the post-RYGB hypoglycemia syndrome is a lack of pancreas samples from asymptomatic subjects with surgery. Moveover, two lines of evidence suggest that prandial hyperinsulinemia is not due to an increase in β-cell mass. First, the syndrome has been corrected by reoperation, either to increase gastric restriction (260) or reverse the RYGB (264). Second, subjects with hypoglycemia after RYGB have comparable insulin secretion in response to IV glucose as for control subjects without surgery (265), suggesting that they do not have generalized β-cell hyperfunction. Thus, although at present several hypotheses speak to the causative mechanisms for hyperinsulinemic hypoglycemia after RYGB, none has been definitively established.

Glucagon secretion following bariatric surgery

A surprising but now well-established finding is that patients with RYGB, BPD, or VSG, as well as rodents with VSG (93), have significant increases in circulating glucagon following meal ingestion (93, 266–268). The profile of prandial glucagon in surgical patients follows closely the temporal pattern of GLP-1 secretion (217, 244), leading to conjecture that enteroendocrine L-cells produce and secrete glucagon after RYGB. However, a recent report suggested that elevated plasma glucagon in surgical patients may be an assay artifact due to increased concentrations of cross-reacting proglucagon peptides (269). It is noteworthy that plasma glucagon levels in subjects with RYGB more than double after a mixed nutrient meal, but they do not increase further with postprandial hypoglycemia (217). These findings suggest substantial changes in α-cell function in these people, possibly leading to defective counterregulation. α-Cell function following surgery has not been well characterized, but the more extreme glucose excursions in surgical patients after meals may be accounted for in some measure by defective glucagon secretion or action.

GLP-1 and the incretin effect following bariatric surgery

The rapid GI transit that is one of the proximal results of RYGB and VSG has dramatic effects on GI hormone secretion (Fig. 3). A hallmark of both procedures is the huge increases in GLP-1 release after meals (Fig. 3). Prandial GLP-1 levels rise ~2-fold in humans with intact GI tracts, but after surgeries that speed gastric emptying the peptide increases to 10-fold and more above basal concentrations (267, 270–272). The increase in circulating GLP-1 after surgery is likely a function of more rapid passage of nutrients into the intestine because GLP-1 release has previously been demonstrated to be more sensitive to the rate, rather than the amount, of nutrient entry into the intestine (273–275). Exemplifying this point, AGB, which does not enhance nutrient delivery to the absorptive surface of the gut, has minimal effect on GLP-1 secretion compared with controls without surgery (276). The case with BPD is more complex. These patients do not have the dramatic changes in prandial glucose that mark VSG and RYGB, but they do experience elevated meal-induced GLP-1 concentrations (161, 202, 219) presumably due to increased rates of enteral nutrient flow through the small bowel.

GLP-1 is produced primarily by enteroendocrine L-cells that are distributed in a graded fashion throughout the intestine, with fewer cells in the upper gut, and the highest concentration in the ileum and colon. However, this distribution is modified following bariatric surgery. Following an RYGB a dense population of L-cells begins to appear in the Roux limb of the small intestine (277), the portion of the mid-jejunum anastomosed to the gastric pouch. Conversely, after VSG, L-cells are generated in greater density in the upper jejunum (277). Thus, it appears that there is a rearrangement of enteroendocrine cells within the GI tract that differs depending on the surgical procedure performed, but these modified distributions are consistent with increased GLP-1 secretion.

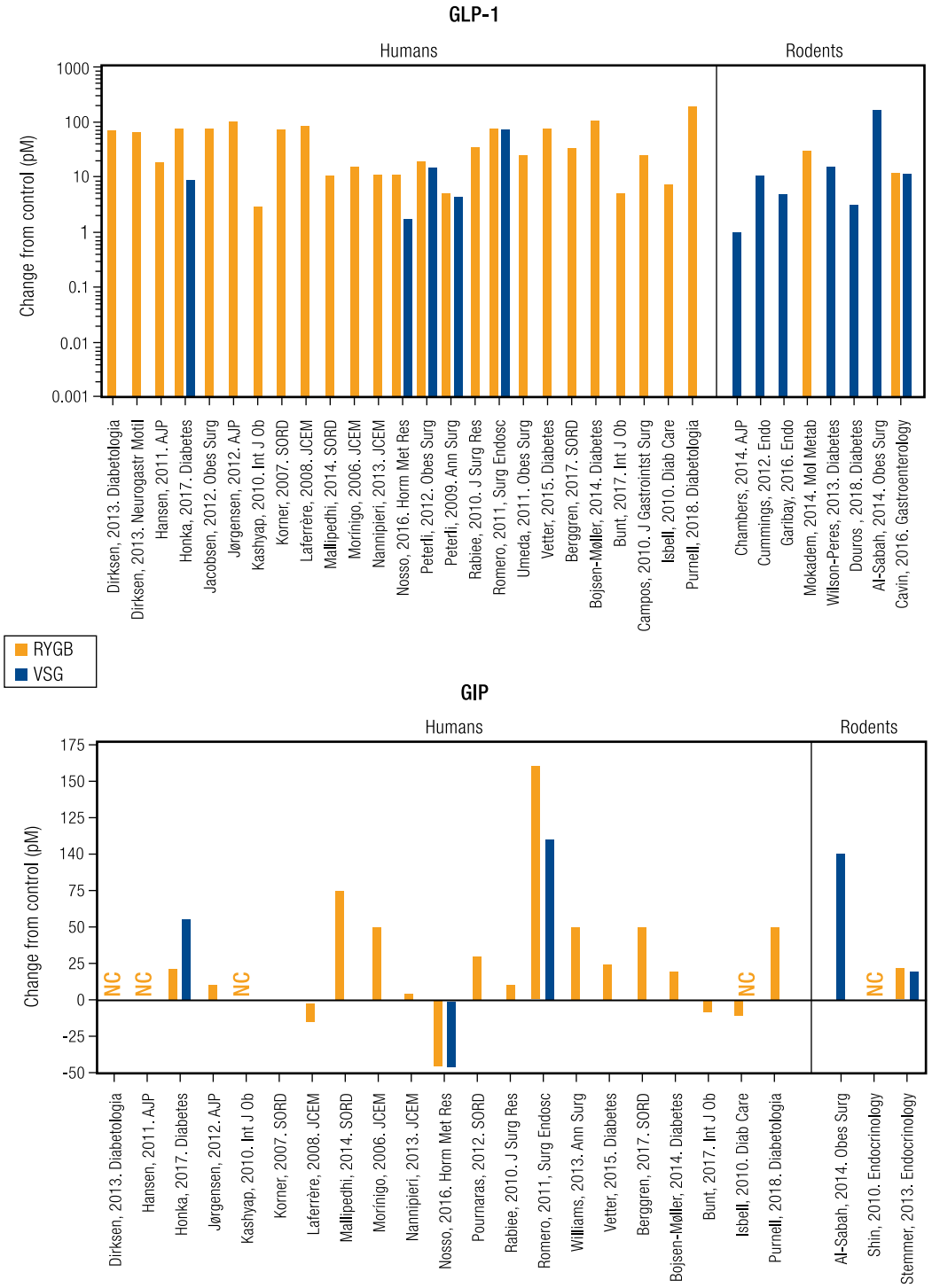


Figure 3. Incretin secretion after RYGB or VSG. GLP-1 (top) and GIP (bottom) secretion following RYGB (red bars) and VSG (blue bars). Data are presented as change relative to control subjects in studies of humans and rodents. References for each study are cited below.

The incretin effect is potentiated following RYGB (278, 279), an effect that has been attributed in great part to GLP-1. In a comparison of nondiabetic RYBG and weight-matched control subjects without surgery, insulin secretion to IV glucose stimulation was similar between groups. However, insulin release in response to ingested glucose was substantially greater in the RYGB group, even when circulating glucose was matched by a glucose clamp (229). In this experimental setting, GLP-1R blockade caused a twofold to threefold greater reduction of insulin secretion in postsurgical subjects compared with a control group with an intact GI tract and significantly lower plasma GLP-1 concentrations. These findings demonstrate that higher prandial GLP-1 secretion following RYGB is associated with an enhanced GLP-1 effect on β-cell function.

The high levels of meal-induced GLP-1 and augmented GLP-1–stimulated insulin secretion among RYGB subjects raises the question of whether these effects can account for the dramatic improvement in glucose regulation in patients with diabetes undergoing surgery. In fact, this does not appear to be the case. Meal-induced GLP-1 did not vary among subjects who had remission of preexisting T2DM and those who remained diabetic following either RYGB (280) or VSG (281). Moreover, five studies have examined the impact of GLP-1 on postsurgical glucose control during meal tolerance tests with and without GLP-1R blockade (281–285). In these studies treatment with the GLP-1R antagonist exendin-(9–39) impaired glucose tolerance in subjects with RYGB (282–285) or VSG (281), but not to a greater degree than before surgery, or in comparison with nonoperated control subjects [Fig. 4(a)]. The lack of a disproportionate exendin-9 effect on glucose homeostasis after surgery indicates that GLP-1 signaling is not the primary mediator of improved diabetes (286). Although GLP-1 does not seem to account for the greater glucose tolerance among patients with diabetes after surgery, it does contribute significantly to the increased insulin secretion seen after RYGB or VSG [Fig. 4(b)]. In every study where postsurgical subjects with diabetes were given exendin-9, prandial insulin was disproportionately reduced (281–285). Similar findings have been reported in nondiabetic subjects with RYBG (229). This discrepant set of responses to GLP-1R blockade in postbariatric surgery patients, that is, a significant diminution of insulin secretion but no effect on acute glucose regulation, has not been explained. However, the reproducibility of the finding is clear. It is plausible that glucose disposition after surgery is not a linear function of circulating insulin, or that there are compensatory mechanisms that maintain homeostasis independent of β-cell secretion.

Secretion of GIP and other GI peptides

It is noteworthy that the secretion of GIP, the other major incretin, after bariatric surgery is still a matter of debate. Postprandial GIP levels have been reported as increased, decreased, or unchanged in RYGB subjects (180, 218, 278, 287). Most of the K-cells that produce and release GIP are located in the duodenum and upper jejunum, regions that are bypassed with RYGB. However, in subjects receiving supplemental feeding through gastrostomy tubes after surgery, GIP responses were comparable whether a test meal was administered into the remnant stomach and bypassed the upper gut or was taken orally into the Roux limb (288). These findings suggest adequate distribution of K-cells throughout the small intestine to maintain GIP release, and, in fact, these cells are increased in the postgastroenterostomy mucosa 10 to 12 months after gastric bypass (289, 290). Although subjects with RYGB maintain a degree of GIP release that is only modestly higher or lower than normal, these changes in no way approach the enormous increase in GLP-1 that is a hallmark of this procedure.

There is much less information about GIP release after VSG. Because GIP release has been described as a linear function of enteral glucose delivery (273), and because subjects with VSG have increased rates of nutrient entry into the upper GI tract, a logical

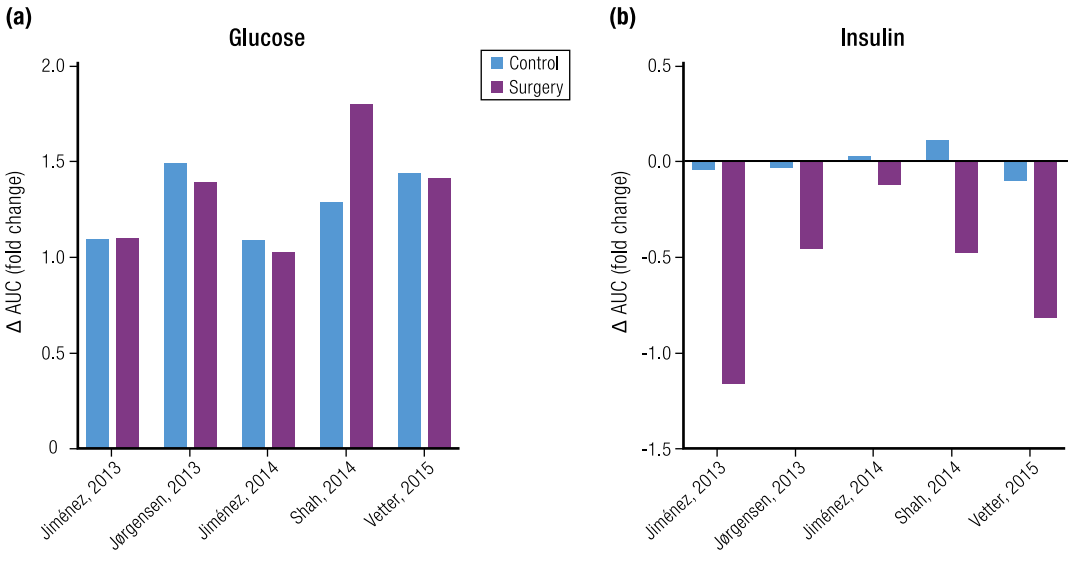


Figure 4. Effects of GLP-1R blockade with exendin-(9–39) in subjects with diabetes with and without RYGB or VSG. (a) The effect of Ex-9 on glycemic responses to meal tests is shown for five separate studies. There is little difference in the magnitude of glucose intolerance induced by exendin-9 in subjects with or without surgery. (b) The effect of exendin-9 on insulin responses to meals. Insulin secretion after GLP-1R blockade was less in subjects with surgery than in controls. The surgical patients in Jiménez 2014 had VSG; the surgical groups in the other studies had RYBG.

inference would be that they would have higher prandial levels of this incretin. However, the limited information that is available does not support this hypothesis, and GIP secretion is unchanged compared with preoperative or nonoperated subjects in most postsurgical subjects (180, 209) (Fig. 3). The prandial secretion of GIP is reduced after BPD (201, 219).

In addition to uncertainty about the relative amounts of GIP secretion following bariatric surgery, the role of GIP receptors on α-cells and β-cells to modulate islet function in postoperative patients remains almost wholly unexplored. The lack of information regarding GIP action after surgery is an important gap in the knowledge base that could explain some of the changes in insulin secretion among patients with T2DM. Although the insulinotropic actions of GLP-1 are moderately attenuated in persons with diabetes (291), the β-cell response to GIP in this group is almost entirely absent (292–296). Insulin treatment to improve HbA_{1c} can restore β-cell sensitivity to GIP (297, 298), as well as the incretin effect (299), in subjects with T2DM. This specific and correctable defect in incretin action among patients with diabetes and the particular effectiveness of bariatric procedures to restore insulin secretion in this group raise the possibility that at least some of the effects of surgery are mediated by GIP. This hypothesis is testable using similar approaches to those used to define the role of GLP-1 in bariatric surgery.

A number of other insulinotropic gut peptides are also known to be differentially regulated following surgery. Gastrin secretion decreases after RYGB and increases with VSG in humans (185, 187, 300, 301). Secretion of peptide YY and cholecystokinin is increased after VSG and RYGB (300, 302, 303). Postprandial pancreatic polypeptide and somatostatin did not change following RYGB (187), whereas other studies show that fasting pancreatic polypeptide is decreased following both RYGB and VSG (185). Rats with BPD have been reported to have increased cholecystokinin and ghrelin cell content in the ileum; however, there are no data regarding the secretion of these peptides in humans or rodents after this surgery (304). The role these factors play in normal physiology is not established in any depth, and their impact after bariatric surgery is unknown.

Other humoral factors influencing islet function

A number of islet-regulating hormonal factors and metabolites change in the context of either an OGTT or MMTT following bariatric surgery. None of these has been characterized as thoroughly as GLP-1, but they are worth mentioning to provide a thorough overview of how modified gut anatomy may affect islet function. Surgery generally decreases free fatty acids and cholesterol (228, 305, 306); it is curious that RYGB-induced, postprandial hypoglycemia correlates with high triglycerides (307). BPD decreases adipocyte lipolysis within 3 days and improves the sensitivity of adipocytes to insulin (197); RYGB also has a rapid effect to enhance adipocyte insulin sensitivity (158).

Protein digestion and absorption increase after RYGB in humans (74). Amino acids, including the metabolically important branch-chain amino acids (BCAAs), display rapid rates of appearance and clearance similar to glucose (308). BCAAs are reduced in nondiabetic subjects after weight loss from RYGB and AGB (309, 310), but not in subjects with weight loss from dietary restriction (310). Increased plasma concentrations of BCAAs have been associated with insulin resistance (311), and this relationship was observed in subjects with RYGB and AGB (309).

Plasma bile acids increase twofold in subjects who have had RYGB, but they do not change following AGB (241, 312). Although proposed to account for some of the weight loss–independent effects of RYGB on metabolism (313), there was no association of bile acid concentrations with insulin secretion or insulin sensitivity among nondiabetic subjects who had lost 20% of body weight with RYGB (312).

Insights From Preclinical Studies of Bariatric Surgery

Surgical effects on body weight and food intake in preclinical models

A number of preclinical, mostly rodent, models of bariatric surgery have been developed. The systemic physiology of these rodent models is largely consistent with surgery in human subjects. These studies, and particularly the application of surgery in mouse genetic models, has allowed testing of more refined mechanistic hypotheses of bariatric surgery. However, there are several features of preclinical models that need to be considered when extending the results to humans (272, 314, 315). Rodent studies generally implement high-fat feeding regimens for 2 to 4 months in genetically identical animals under controlled conditions to achieve obesity and relative glucose intolerance (316, 317). This represents a relatively acute, homogeneous metabolic challenge, whereas humans are subject to decades of lifestyle, genetic, and environmental factors that contribute to the development of obesity and diabetes (318). Rodents given either bariatric or sham surgery lose up to 20% of their body weight during a matter of weeks before returning to a trajectory of weight gain parallel to, but never returning to, that of control animals fed *ad libitum* (177, 271, 314). This is an accelerated version of the dynamics of weight loss in humans who have maximal weight loss during 6 to 12 months before reaching a plateau or slow weight regain (8). The rapid weight loss observed in rodent studies improves glucose control in both treatment and sham-operated control groups in the early

postoperative time period. A key benefit available for experiments with preclinical models is the ability to pair-feed a sham-operated control group, allowing matched caloric intake and generally comparable body weights to animals receiving surgery. This allows a more direct test of effects of surgery that are independent of energy balance, a key question raised in human research of bariatric surgery.

Food consumption is initially reduced after bariatric surgery in rodents (319). However, mice subjected to VSG subsequently increase their caloric intake to similar levels as controls within 2 weeks of surgery, even though their preference shifts toward less energy-dense foods (319). Lean body mass tends to increase, whereas fat mass is reduced, after surgery (319, 320). The mechanisms underlying this effect are unknown but raise the possibility that these models could be used to identify novel therapeutic targets. Rats given either RYBG or VSG, and mice with VSG, have lower fasting blood glucose compared with sham-operated controls (302, 321, 322). Fasting blood glucose is often lowered in a weight-independent manner in rodents when comparisons are made to weight-matched and/or pair-fed animals (302, 321). Alternatively, rats given an AGB have no change in fasting blood glucose (323). This suggests a weight-independent enhancement of insulin sensitivity and/or reduction in HGP after procedures that have been more effective for diabetes resolution in humans. There is a need for further research regarding changes to nutrient handling in critical tissues such as the liver after bariatric surgery, as well as how these changes are integrated at the level of the islet to modify basal glucose levels.

Surgical effects on glucose control and insulin secretion in preclinical models

Similar to nearly all available human data, glucose tolerance is changed in response to either a glucose or mixed-nutrient gavage in rodents after surgery, frequently with a more rapid initial excursion but an overall reduction in glycemic exposure (*i.e.*, glucose area under the curve) (93, 177, 210, 324–326). This glycemic response is accompanied by elevated plasma insulin (177, 210, 324, 325) and higher plasma concentrations of postprandial GLP-1 (93, 272, 326, 327); the latter has been associated with increased rates of enteral nutrient flux after surgery in rodents (328, 329). Additionally, postgavage GIP appears to be elevated after VSG in rats and mice, suggesting hyperstimulation of duodenal K-cells after this procedure (93, 330), whereas GIP secretion after RYGB is mixed, with some studies reporting elevated levels (330) and others no change (303). Notably, many studies demonstrate improved glucose control during either IP or IV glucose tolerance tests, which bypass the surgically modified gut and do not affect secretion of incretins (93, 326, 331). These findings are in keeping with those in humans with diabetes and suggest that surgery causes changes in the β-cell responsiveness to glucose that are independent of acute stimulation by gut factors. Indeed, a recent study by Douros *et al.* (93) demonstrates that pancreatic islets isolated from mice with a VSG undergo intrinsic changes within a week of surgery that sensitize the insulin response to glucose and uniquely modify the transcriptomic profile compared with calorically restricted, weight-matched controls. It is unclear how the changes in GI anatomy are communicated to the islet to evoke these changes.

Mechanistic studies in mice with candidate gene deletions

A number of studies have been reported where genetic mouse lines, particularly those with single gene knockouts, were used to test specific mechanisms underlying the metabolic benefit of bariatric surgery. This candidate gene approach is highlighted by several studies utilizing GLP-1R knockout models, a logical choice given the consistently high circulating levels after surgery and potent actions for glycemic reduction. In two studies with VSG (320, 326) and one with RYGB (177), deletion of the GLP-1R did not attenuate the benefit of surgery on weight loss or glucose tolerance, suggesting that other mechanisms compensate, or substitute, for the absence of GLP-1 signaling. A single study of VSG in mice with a β-cell deletion of the GLP-1R did show a modest reduction of the surgical effect on glucose tolerance (332).

Beyond the studies of GLP-1R knockout lines, it has been shown that ghrelin (331), the GLP-2 receptor (333), acyl CoA:monoacylglycerol acyltransferase-2 (MGAT2) (334), Magel2 (a Prader–Willi syndrome model) (335), gustducin (177), apo AIV (329), serotonin (336), and lipocalin-type prostaglandin D_2 (L-PGDS) (335) are dispensable for the glycemic benefits of VSG. The effect of the bile acid–binding receptor TGR5 is not required for glucose lowering after RYGB (337), but it may contribute to the glucose lowering response after VSG (338). Conversely, leptin appears to be required for improving glycemic control after RYGB in mice (339), as *ob/ob* animals given surgery failed to improve glucose tolerance, insulin sensitivity, and hyperinsulinemia despite weight loss (339). Perhaps the best example of a single factor with an effect to mediate the actions of VSG is the farnesoid-X receptor (FXR, a nuclear bile acid receptor) (316). Mice with a global deletion of this gene failed to lose weight or improve glucose tolerance after surgery. However, this model has some limitations in that the knockout mice were leaner than wild-type controls and had better glucose tolerance prior to surgery.

Overall, studies with rodent models have provided some valuable insights into the physiology of bariatric surgery and should continue to augment clinical research in this area. Ongoing technical refinements and more widespread availability and expertise will enhance the applications and breadth of questions that

can be tested in animal models. The published literature to date indicates that improved glucose homeostasis after surgery is unlikely to be mediated by single gene products, whether they be receptors, their ligands, or other regulatory factors. Rather, the view from preclinical work suggests more complex mechanisms that involve the interplay of a number of mediators and systems. Preclinical models are amenable to unbiased discovery methods such as gene transcription analysis, metabolomics, and proteomics that are useful for interrogating complex systems, and it is easy to foresee these sorts of approaches leading to important advances in the future.

Conceptualizing the Potential Mechanisms for Surgery to Improve Glucose Control

Connecting anatomic modifications of surgery to islet function

Work during the last century has demonstrated that surgery to the GI tract has multiple, potent actions on metabolic physiology. However, only recently have these procedures been sufficiently standardized to allow for a comparison of effects between surgical approaches. Even with widespread clinical use of RYGB and VSG, and to a lesser degree AGB and BPD, there have been few studies designed to compare and contrast the effects of various surgically revised GI anatomies. The bulk of evidence suggests that AGB works mainly through decreasing food intake, with few of the changes seen with the other procedures such as GI motility, absorption, and hormone secretion. Indeed, AGB has been applied in comparisons with RYGB in a manner similar to dietary and lifestyle measures under the assumption that it has few effects beyond reduction of caloric consumption (189, 340).

It is also clear that BPD causes significantly more malabsorption than do the other bariatric procedures, and in fact it may cause effects that are independent of a diet based on the limitations imposed on enteral nutrient uptake (108). However, there are several other features of the BPD that also distinguish this surgery from the others. First, the larger gastric remnant (300 mL compared with ~30 mL for RYGB and ~100 mL for VSG and BPD-DS) and distal gastrectomy (341) may actually delay rather than accelerate passage of nutrients through the gut (89), although this is not true of BPD-DS (69). Second, the resolution of insulin resistance seems to be faster for BPD than for the other procedures, with unequivocal improvement after 1 week (201). Third, the improvement of insulin secretion after surgery does not seem to be as great for BPD as for VSG and RYGB (180, 201), although this may be partly due to adaptation for a greater degree of insulin sensitivity. Interestingly, the DI undergoes greater enhancement after BPD-DS than after VSG in the only study comparing the two (211). Notably, responses that are consistently enhanced by RYGB such as insulin clearance and the incretin effect are only minimally affected by BPD (113). Finally, although the GLP-1 response is enhanced approximately twofold after BPD (161, 197, 211), it does not appear to be as substantial as in patients with VSG and RYGB, whereas GIP seems to be significantly reduced, an observation unique to this surgery (201, 219). These examples cannot be considered definitive in the absence of more direct comparisons in well-defined surgical groups. However, the differences support distinct mechanisms of action for specific surgical manipulation and support comparative studies with robust physiologic testing.

It is notable that VSG and RYGB, two procedures that have major differences in postsurgical anatomy, have the most comparable acute and chronic effects on glucose metabolism and weight loss. Although the results of one study suggest that enhanced insulin secretion in the early postoperative phase may be greater with VSG (99), there is insufficient evidence to draw more distinctions between the two procedures. What is notable is that VSG and RYGB share the effect of greatly accelerated passage of ingested nutrients into the intestine, with the rapid absorption of glucose, amino acids, and other small molecules challenging

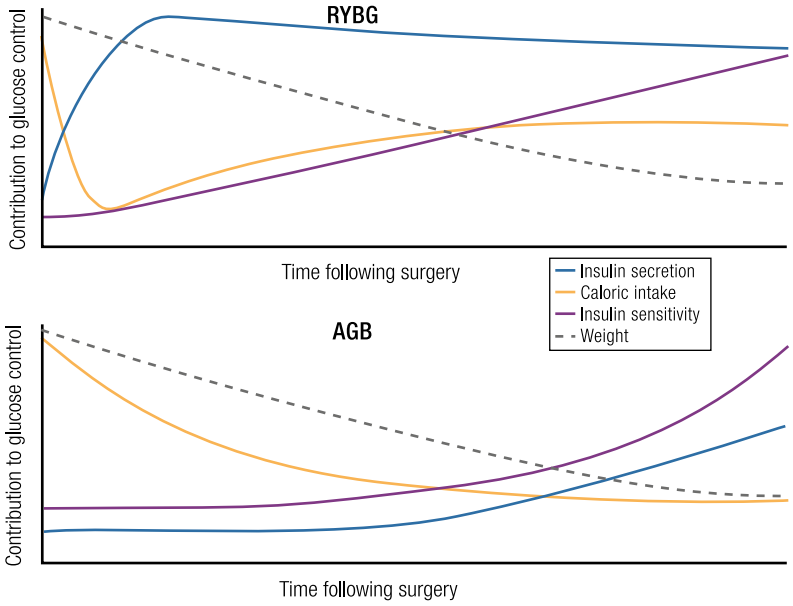


Figure 5. Schematic of a hypothetical model of adaptations of insulin secretion and insulin sensitivity after RYGB and AGB. Against a background of decreased caloric intake and decreasing body weight, parameters of glucose metabolism have varying courses with RYGB and AGB. As body weight decreases, insulin sensitivity improves after body surgeries. In nondiabetic subjects, insulin secretion is fairly static after AGB, but with the significant increase of insulin action the DI improves slightly in nondiabetic subjects. Following RYGB enhanced incretin stimulation leads to greater insulin responses; in subjects with diabetes, FPIR is restored and secretion after meals is also improved. Over time, as weight loss progresses, there is a decrease in the absolute amount of insulin released among nondiabetic subjects, although the DI improves. The dampening of the β-cell response after RYGB compensates for greater insulin sensitivity, mitigating the risk of hypoglycemia. See (165, 168, 185, 213).

homeostasis with each meal. The need to adapt to this challenge may provide the impetus for physiologic changes that improve glucose metabolism (65). Research to determine whether these two procedures have distinct or shared mechanisms of action on glucose tolerance would provide a major advance.

More direct and refined comparisons of the physiologic changes following different bariatric procedures, interpreted in the context of surgical anatomy, are likely to provide insight into the mechanisms by which VSG, RYGB, and BPD act. Inclusion of measures of GI motility and substrate absorption are important for this sort of investigation because meal appearance of substrates is important for assessing systemic fluxes and may in fact play a role in initiating metabolic mechanisms. This line of investigation would also benefit from validation of simple metrics such as HOMA modeling and the DI among the various procedures, as well as from a rigorous test of the relationship between insulin clearance and insulin sensitivity.

Temporally dynamic model

There are longitudinal data available to suggest that processes involved in glucose regulation change and adapt over time after surgery. There is also evidence for adaptation of intestinal histology and function (70, 224). Although the temporal profile of adaptations cannot be mapped with great detail, a general description is possible (Fig. 5). Initial reductions in glycemia and insulin concentrations seem to be driven in great part by decreased caloric intake. At least with VSG and RYGB, there appears to be an enhancement of β-cell function in the first postoperative month, mostly as a result of increased enteral stimulation of insulin secretion. This heightened β-cell function is concomitant with small, gradual suppression of HGP, possibly driven by increased hepatic insulin action. These early phenomena could contribute to what has been termed weight loss ($<$15%)–independent effects of surgery, although they occur in a setting of negative energy balance. As the postoperative time frame progresses and patients begin to lose substantial amounts of weight, there are detectable changes in global insulin sensitivity, and insulin secretion is dampened to accommodate this, even when the DI is ultimately relatively increased. The likelihood that the response to surgery evolves over time is an important consideration for the design of experiments, where the timing of cross-sectional comparisons or longitudinal measures might be expected to impact outcomes.

Summary

The last 20 years have seen a sharp rise in the clinical application of bariatric surgery. There has been growth in the number of surgeons specializing in the treatment of obesity and diabetes, a refinement and standardization of procedures, and an increase in the acceptance and utilization of surgery across the spectrum of health care providers and payers. A parallel rise has also occurred in the depth and quality of research focused on bariatric surgery, with much of the work addressing its effects on diabetes. Data from carefully done observational studies have now been bolstered by results from randomized clinical trials to provide a clearer picture of safety, efficacy, and outcomes. Valuable subdomains of bariatric surgery research have also grown and developed, including applications of epidemiology, quantitative modeling, and health economics.

There has also been progress in understanding the physiology underlying the mechanisms whereby surgery affects glucose metabolism, processes fundamental to the treatment of diabetes and the focus of this review. The large effects of surgery to quickly reduce diabetic hyperglycemia are one of the most dramatic shifts of metabolism in clinical medicine. Although decreased caloric consumption and negative energy balance play an important role in the factors leading to diabetes resolution, there is solid evidence that surgery also changes parameters such as insulin secretion and regulation of HGP, which can reduce glycemia. Understanding how surgery to the GI tract co-opts normal physiology to amplify glucose clearance is an area of clinical investigation that is still at an early stage. However, the potential for research in this area seems very promising because the dramatic effects of surgery suggest underlying mechanisms that are central to metabolic physiology and could serve as therapeutic targets. The state of current knowledge in this area is sufficient to support the design and application of larger, more powerful studies directed at specific mechanisms affected by surgery. This is arguably the next frontier in the application of surgery to treat diabetes.

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Abbreviations

AGB, adjustable gastric band; BCAA, branched-chain amino acid; BMI, body mass index; BPD, biliopancreatic diversion; BPD-DS, BPD with duodenal switch; DI, disposition index; FPIR, first phase insulin release; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor; HbA_{1c}, glycated hemoglobin; HGP, hepatic glucose production; HOMA, homeostasis model assessment; HOMA-S, HOMA of insulin sensitivity; ISR, insulin secretion rate; MMTT, mixed meal tolerance test; OGTT, oral glucose tolerance test; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; STAMPEDE, Surgical Treatments and Medication Potentially Eradicate Diabetes Efficiently; T2DM, type 2 diabetes mellitus; VLCD, very low-calorie diet; VSG, vertical sleeve gastrectomy.