Mechanisms of Diabetes Improvement Following Bariatric/Metabolic Surgery

Rachel L. Batterham[1,2,3] and David E. Cummings[4]

Diabetes Care 2016;39:893–901 | DOI: 10.2337/dc16-0145

More than 20 years ago, Pories et al. published a seminal article, "Who Would Have Thought It? An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus." This was based on their observation that bariatric surgery rapidly normalized blood glucose levels in obese people with type 2 diabetes mellitus (T2DM), and 10 years later, almost 90% remained diabetes free. Pories et al. suggested that caloric restriction played a key role and that the relative contributions of proximal intestinal nutrient exclusion, rapid distal gut nutrient delivery, and the role of gut hormones required further investigation. These findings of T2DM improvement/remission after bariatric surgery have been widely replicated, together with the observation that bariatric surgery prevents or delays incident T2DM. Over the ensuing two decades, important glucoregulatory roles of the gastrointestinal (GI) tract have been firmly established. However, the physiological and molecular mechanisms underlying the beneficial glycemic effects of bariatric surgery remain incompletely understood. In addition to the mechanisms proposed by Pories et al., changes in bile acid metabolism, GI tract nutrient sensing and glucose utilization, incretins, possible anti-incretin(s), and the intestinal microbiome are implicated. These changes, acting through peripheral and/or central pathways, lead to reduced hepatic glucose production, increased tissue glucose uptake, improved insulin sensitivity, and enhanced β-cell function. A constellation of factors, rather than a single overarching mechanism, likely mediate postoperative glycemic improvement, with the contributing factors varying according to the surgical procedure. Thus, different bariatric/metabolic procedures provide us with experimental tools to probe GI tract physiology. Embracing this approach through the application of detailed phenotyping, genomics, metabolomics, and gut microbiome studies will enhance our understanding of metabolic regulation and help identify novel therapeutic targets.

REGULATION OF GLUCOSE HOMEOSTASIS: HISTORICAL INSIGHTS FROM GASTROINTESTINAL SURGERY

Impaired glucose homeostasis is characterized by a combination of insulin resistance and defective β-cell function that worsens with time. Blood glucose levels rise, and type 2 diabetes mellitus (T2DM) ensues only when β-cells are incapable of releasing sufficient insulin to compensate for prevailing insulin resistance (1). Genome-wide association studies have identified that β-cell dysfunction has a clear genetic component (2). However, environmental factors also influence insulin resistance and β-cell function. In recent years, the remarkable effect of bariatric surgery on glucose regulation has helped identify key glucoregulatory roles for the gastrointestinal (GI) tract.

[1]*Centre for Obesity Research, Department of Medicine, University College London, London, U.K.*
[2]*Bariatric Centre for Weight Management and Metabolic Surgery, University College London Hospital, London, U.K.*
[3]*National Institute for Health Research, Biomedical Research Centre, University College London Hospital, London, U.K.*
[4]*VA Puget Sound Health Care System and Diabetes and Obesity Center of Excellence, University of Washington, Seattle, WA*

Corresponding author: Rachel L. Batterham, r.batterham@ucl.ac.uk.

Received 22 January 2016 and accepted 21 March 2016.

See accompanying articles, pp. 857, 861, 878, 884, 902, 912, 924, 934, 941, 949, and 954.

The notion that rerouting the GI tract alters glycemia is not new, with reports in the 1930s of altered glucose tolerance curves in patients after GI surgery for peptic ulcer disease (3). In 1942, Evensen described alimentary hypoglycemia that was observed several years after peptic ulcer disease surgery, and he proposed increased insulin sensitivity as the underlying mechanism (4). Interestingly, these hypoglycemic accounts are strikingly similar to the hypoglycemia experienced by a minority of patients after Roux-en-Y gastric bypass (RYGB).

Bariatric surgical procedures were developed in the 1950s to reduce body weight. Since the 1970s, however, there have been anecdotal reports of rapid postoperative T2DM remission. In 1984, bariatric surgery was reported to improve glucose tolerance in insulin-treated severely obese patients (5). In a 1992 article, "Is Type II Diabetes Mellitus (NIDDM) a Surgical Disease?", Pories et al. reported T2DM reversal in 78% of patients who underwent gastric bypass (6). However, it was their subsequent article in 1995, "Who Would Have Thought It? An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus," that catalyzed research into identifying the mechanisms by which bariatric surgery improves glucose homeostasis and promotes T2DM remission (7).

Historically, bariatric operations were thought to promote weight loss by causing gastric restriction and/or malabsorption. However, newer mechanistic studies, in parallel with establishment of the GI tract as a key regulator of energy and glucose homeostasis, have made it clear that alternative mechanisms primarily mediate the weight-reducing and antidiabetes benefits of most bariatric/metabolic operations. Discrete parts of the GI tract differentially influence glucose homeostasis; hence, the underlying mechanisms contributing to improved glucose tolerance and clinical outcomes undoubtedly differ among anatomical procedures (displayed in Fig. 1). Indeed, T2DM remission rates differ according to surgery type: lowest for laparoscopic adjustable gastric banding (LAGB) and highest for biliopancreatic diversion (BPD) (8).

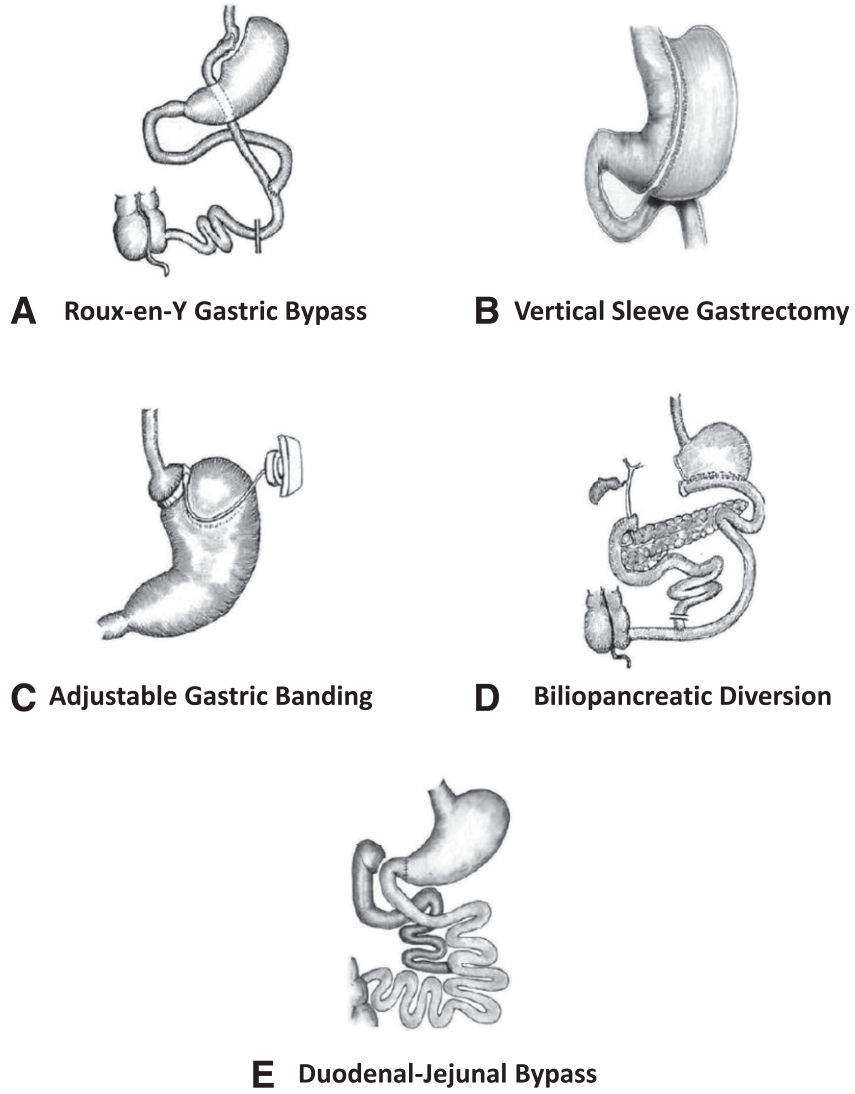

Figure 1—Bariatric/metabolic operations discussed in this article. *A*: RYGB. The stomach is divided into two compartments, leaving only the small upper chamber in digestive continuity. Food passes from there to the proximal jejunum, bypassing most of the stomach, the duodenum, and a small portion of jejunum. *B*: VSG. Most of the stomach (primarily the body and fundus) is excised, leaving a narrow sleeve along the lesser curvature. Nutrients follow the normal route through the GI tract. *C*: LAGB. An inflatable silicon ring encircling the upper stomach is serially adjusted to optimize the diameter of a tight aperture that hinders food flow. *D*: BPD. A large majority of the small intestine is bypassed, purposely causing malabsorption. *E*: DJB. A modest segment of proximal intestine is bypassed, as in RYGB, without compromising gastric capacity.

OVERVIEW OF ROLES OF THE GI TRACT IN REGULATING ENERGY AND GLUCOSE HOMEOSTASIS

The presence of nutrients in the GI tract triggers a complex series of hormonal and neural responses that regulate energy and glucose homeostasis. Gut peptides are synthesized and secreted from enteroendocrine cells of the epithelial mucosa. For example, I cells and K cells of the proximal intestine primarily produce cholecystokinin and glucose-stimulated insulinotropic polypeptide (GIP), respectively, while L cells of the distal intestine primarily produce glucagon-like peptide 1 (GLP-1), GLP-2, oxyntomodulin, and peptide YY (PYY)—most of which contribute to satiation and/or satiety. Gut peptides and nutrients act on peripheral and central targets via the circulation and/or through afferent nerves. Oral glucose promotes greater insulin release than does isoglycemic glucose administered parenterally, a phenomenon known as the incretin effect, which is predominantly mediated by the incretins GLP-1 and GIP. These peptides enhance glucose-stimulated insulin secretion, insulin action, and β-cell function. Patients with T2DM exhibit a blunted incretin effect, coupled with attenuated GIP

action and reduced circulating GLP-1 levels (9). From results based largely on animal experiments, some investigators have postulated the existence of anti-incretins: putative nutrient-stimulated GI neuroendocrine signals emanating from the proximal gut to counterbalance the effects of incretins and other postprandial glucose-lowering mechanisms (10). The findings that proteins secreted from the small intestine of diabetic (but not nondiabetic) rodents induce muscle insulin resistance in cell-based assays and in vivo support this concept and are consistent with preliminary human observations (11). Although specific human anti-incretins have not yet been clearly identified, a strong candidate was recently discovered in *Drosophila* (limostatin, named a decretin by these investigators) (12).

From results based primarily on mechanistic animal studies plus complementary associative observations in humans, bile acids (BAs) are now believed to be important regulators of energy balance and metabolism, primarily via the nuclear farnesoid X receptor (FXR) and the G-protein–coupled receptor TGR5 (13) (Fig. 2). Postprandially, BAs are released into the duodenum to mix with ingested nutrients. They are then actively reabsorbed from the terminal ileum and returned via the portal circulation to the liver. A small percentage of BAs are deconjugated by gut bacteria, forming secondary BAs, which are reabsorbed or excreted in feces (14).

The transintestinal BA flux activates intestinal FXR, inducing synthesis and secretion into the circulation of the ileal-derived enterokine FGF-19 (FGF-15 in mice). FGF-19 inhibits expression of cholesterol 7 α-hydroxylase-1 (CYP7A1), the rate-limiting step of BA synthesis (13). In mice, FGF-15 can improve glucose tolerance by regulating insulin-independent glucose efflux and hepatic glucose production. BAs acting via TGR5 stimulate L-cell secretion of GLP-1 and PYY. Directly and indirectly through the FXR-induced antimicrobial peptides, BAs also regulate gut microbiota composition. This, in turn, has been linked to the pathogenesis of obesity and T2DM in rodents, and correlative data in humans are consistent with that. Recently, an orally active gut-restricted FXR agonist was shown to restore glucose homeostasis in mice with diet-induced obesity and glucose intolerance by inhibiting hepatic glucose production (15). Thus, there is complex cross talk among BAs, gut hormones, FGF-19, and the microbiome, which in turn influences glucose homeostasis.

After a meal, nutrients, hormones, and neural signals inform the brain of the current nutritional status. An emerging picture based on animal studies suggests

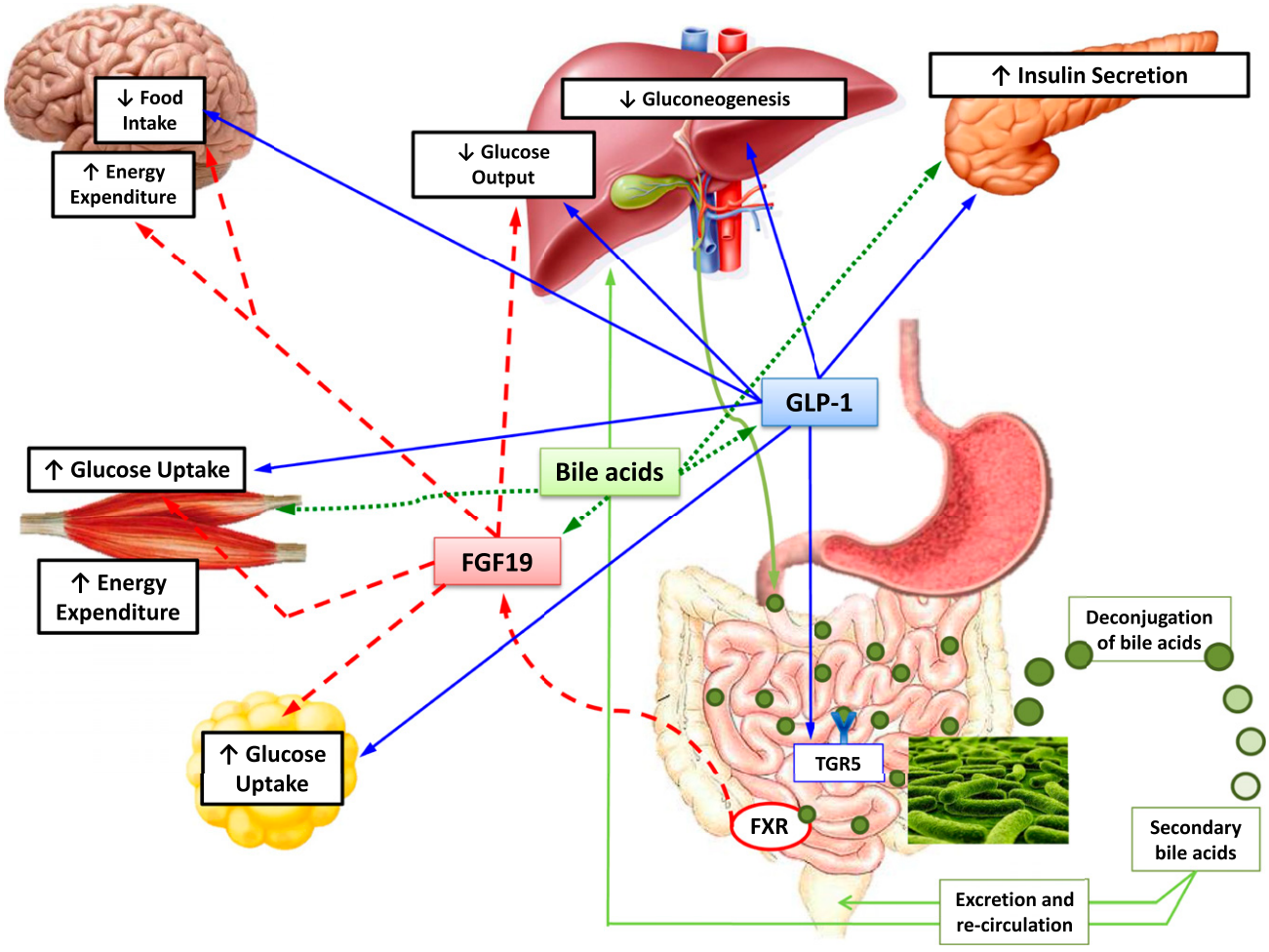

Figure 2—Diagram of some of the metabolic effects and cross talk among BAs, GLP-1, and FGF-19.

that glucose homeostasis may be influenced by a gut–brain–liver axis in which gut-derived signals acting centrally regulate hepatic glucose production (16). Using intraintestinal nutrient infusions in rodents, Lam and colleagues (17,18) demonstrated that the duodenum and jejunum sense nutrients and initiate negative-feedback mechanisms through a gut–brain–liver neuronal axis to regulate glycemia, mainly via reducing hepatic glucose production. Interestingly, studies comparing infusion of nutrients into the midjejunum compared with the duodenum in humans with T2DM revealed that jejunal infusion led to greater insulin sensitivity for glucose and fatty acids (19).

Mechanisms Mediating the Effects of Bariatric/Metabolic Surgery on Glucose Homeostasis

In their seminal article from >20 years ago (7), Pories et al. speculated that the very rapid post-RYGB improvement of glucose tolerance, which typically occurs before significant weight loss, might result from acute caloric restriction plus possible additional consequences of excluding ingested nutrients from the proximal intestine and/or expediting delivery of nutrients to the distal intestine. At that time, Harvey Sugerman's group published that gut hormone changes were more profound after RYGB than the purely mechanical vertical-banded gastroplasty, perhaps helping explain the superior weight-reducing and antidiabetes effects of RYGB compared with vertical-banded gastroplasty (20). Weight-independent antidiabetes effects of proximal intestinal bypass were subsequently demonstrated in rats in a landmark article by Rubino et al. (21) on duodenal-jejunal bypass (DJB), which replicates just the intestinal component of RYGB, and those findings have held up in numerous human studies. Similarly, the beneficial effects of enhanced distal intestinal nutrient exposure were proven in rats with ileal interposition surgery (22), and these too have translated to humans.

In the 20 years since the classic article by Dr. Pories and colleagues, mechanistic knowledge about bariatric/metabolic surgery has greatly expanded, although many issues remain unclear and controversial. This is partly related to methodological issues in patients studied and protocols used, and especially whether test nutrients are administered via the GI tract or parenterally (Table 1). RYGB and vertical sleeve gastrectomy (VSG) (Fig. 1) markedly increase the rate at which ingested nutrients enter the small intestine. Blood glucose levels rise rapidly, achieving earlier and higher peaks, followed by lower nadirs associated with increased GLP-1 and insulin responses. Furthermore, whether studies in rodents can be extrapolated to humans is unclear, given that rodents deplete liver glycogen stores quickly and have a greater capacity for glycogenolysis than humans (23). Proposed mechanisms underlying the glycemic effects of bariatric surgery will now be discussed (Fig. 3).

CALORIC RESTRICTION AND WEIGHT LOSS

Improvement in glucose homeostasis after RYGB, VSG, and BPD typically begins within days of surgery, before significant weight loss occurs. Thus, total body weight loss per se is unlikely to play a significant role in mediating early glycemic improvements. Further evidence for effects independent of weight loss stems from studies showing that RYGB leads to a greater oral glucose tolerance compared with patients with equivalent weight loss after LABG or caloric restriction (24,25). However, the time taken to achieve a given weight reduction with caloric restriction or LABG in these studies was longer than after RYGB, suggesting that the degree of caloric restriction was greater after RYGB and/or that energy expenditure is higher after that operation. Furthermore, RYGB causes rapid passage of oral nutrients into the intestine, with early higher peaks of blood glucose, GLP-1, and insulin, confounding direct comparisons of oral glucose tolerance tests after caloric restriction versus RYGB. To address these issues, Korner and colleagues compared RYGB patients with patients consuming a very low-calorie diet (VLCD, 500 kcal/day) and used frequently sampled intravenous glucose tolerance tests rather than oral meals (26). This approach showed that VLCD and RYGB produced comparable improvements in insulin sensitivity and β-cell function in the absence of acutely elevated nutrient-stimulated GLP-1 levels. These findings suggest that acute postoperative caloric restriction is a significant contributor and that marked energy deficit exerts a glucose-lowering effect independent of weight loss. Others have argued that the inflammatory insult of surgery per se, which is likely to impair insulin sensitivity, makes a direct comparison of VLCD and surgery invalid. Studies by Lingvay et al. suggest that a surgery-related stress response occurs. They compared the effects of VLCD versus RYGB in patients with T2DM, with individuals serving as their own controls. After 10 days of VLCD, there was a significant improvement in fasting glucose, peak glucose, and glucose area under the curve during a mixed-meal challenge test, but not after RYGB, despite a greater GLP-1 response with the latter (27).

Patients with T2DM have increased hepatic fat and pancreatic fat compared with BMI-matched normoglycemic patients (28). Taylor and colleagues found that among patients with T2DM who underwent a VLCD or RYGB, hepatic fat content decreased rapidly in parallel with improved hepatic insulin sensitivity and normalization of fasting plasma glucose levels within 7 days (29). Reduction in pancreatic fat content was slower with both VLCD and RYGB, taking 8 weeks to normalize to nondiabetic levels. Pancreatic fat reduction was accompanied by restoration of the first-phase insulin (29,30). These studies highlight the role of hepatic and pancreatic fat in the pathogenesis of T2DM and also

Table 1—Factors affecting studies examining glycemic effects of bariatric procedures

Sex
Age
Ethnicity
Genetics
BMI and fat distribution
Glycemic status (normoglycemic, impaired glucose tolerance, or T2DM)
Duration of T2DM
Medications (and duration of stopping these before being studied)
Impact of preoperative liver-reducing diet
Stimulus used (oral or intravenous)
For oral nutrient stimuli (energy load, macronutrient composition, liquid/solid, and volume)
Method used to assess glycemic response
Time after surgery

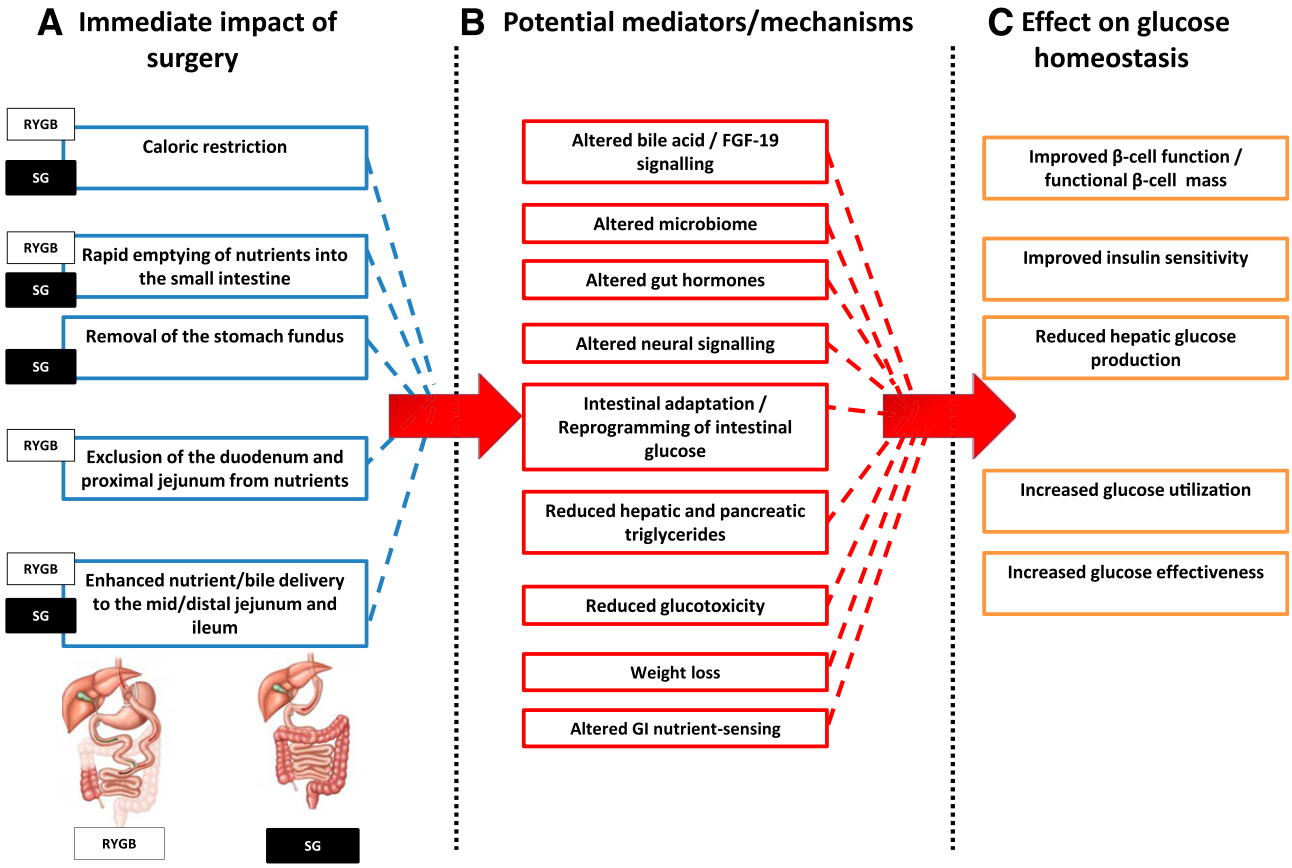

Figure 3—Schematic of potential mechanisms contributing to improved glycemia after RYGB and VSG. *A*: Immediate effects of RYGB and VSG due to anatomical changes. *B*: Potential mediators/mechanisms involved. Cross talk occurs among these factors. *C*: Effects on glucose homeostasis.

the potential of a profound energy deficit to improve T2DM. However, VLCD-induced weight loss leads to compensatory homeostatic changes, including increased hunger, increased circulating ghrelin, and reduced circulating GLP-1 and PYY—changes that are likely to contribute to the high degree of weight recidivism with dieting (31). In contrast, postprandial GLP-1 and PYY levels increase after RYGB and VSG, while ghrelin usually falls. These changes probably contribute to reduced appetite and taste changes that favor ongoing weight loss and weight-loss maintenance (32).

The above studies suggest that β-cell function may not improve until 8 weeks after RYGB. However, using intravenous glucose administration, Martinussen et al. demonstrated enhanced, although not normalized, first-phase insulin response and improved HOMA-β in patients with T2DM within 1 week of surgery (33). These findings suggest that RYGB has an early beneficial effect on β-cell function. The reduced glucotoxicity resulting from normalized glucose levels likely contributes to these changes; however, similar studies with VLCD alone are needed to investigate this.

Most T2DM remission occurs during the first 8 postoperative weeks, whereas some studies report that peripheral insulin resistance improves over a longer time and may be at least partly related to weight loss (30). In the long-term, GLP-1 or other surgery-related mediators might possibly stimulate β-cell regeneration or hypertrophy, which could protect against T2DM recurrence even with weight regain, although this is controversial (see GLP-1).

The role that total weight loss plays in T2DM initial remission and longer-term maintenance of remission is controversial and likely differs among bariatric/metabolic operations. A relationship between the percentage of weight loss (%WL) and T2DM remission rates, which is sometimes but not always observed, can be interpreted in three different ways. Firstly, that %WL plays a role in mediating T2DM remission; secondly, that the presence of T2DM adversely affects weight loss; and thirdly, that common mechanistic factors drive both T2DM remission and weight loss. Furthermore, the relationship between T2DM remission and %WL is likely to vary depending on the duration and severity of T2DM and individual patient characteristics.

GLP-1

It is widely accepted that postprandial circulating GLP-1 levels are markedly elevated after RYGB, BPD, and VSG, together with elevated peak postprandial insulin levels, whereas plasma GLP-1 levels remain unaltered with caloric restriction and LAGB (34). This exaggerated postmeal GLP-1 secretion is present from day 2 postsurgery and persists long-term. The hindgut hypothesis asserts that enhanced delivery of nutrients and/or bile to the distal GI tract, as a consequence of GI anatomical rearrangement, rapid gastric emptying, and/or other factors, leads to increased stimulation of the distal small intestine and colon, with increased nutrient-stimulated

secretion of distal gut peptides. Proof of concept for this theory comes from ileal interposition studies in rodents, where a section of distal ileum is interposed to the duodenum-jejunum boundary while preserving the vessels and nerves supplying the ileal segment. Ileal interposition enhances L-cell nutrient and BA exposure, without gastric restriction or malabsorption, thereby increasing circulating GLP-1 (and PYY) levels, together with improved glucose tolerance. The overall effect of ileal interposition on glucose metabolism and body weight is typically modest, however, suggesting this effect only partly contributes to glycemic improvements (35). Consistent with the hindgut hypothesis, RYGB results in greater GLP-1 and PYY release compared with VSG (36). The physiological relevance of increased GLP-1 secretion in mediating glycemic improvements after RYGB and VSG is contentiously debated with strong protagonists and antagonists. As discussed above, VLCD and RYGB may lead to comparable short-term improvements in hepatic insulin sensitivity and β-cell function when assessed using intravenous glucose administration in the absence of elevated GLP-1 levels. In patients with T2DM, however, full recovery of β-cell function early postsurgery or in patients in clinical remission 3 years postsurgery is observed only with oral rather than with intravenous glucose administration, suggesting that gut-derived factors are needed for full effects (37). Studies using the GLP-1 receptor antagonist exendin(9-39) postsurgery to interrogate the physiological role of exaggerated postoperative GLP-1 levels have yielded opposing findings (partly due to methodological differences outlined in Table 1), and hence, opposing conclusions. Studies using exendin (9-39) in rodents undergoing bariatric surgery suggest a role for GLP-1 in regulating glycemia after VSG (38). However, studies using GLP-1 receptor–null mice and mice with functional deletion of GLP-1 suggest that neither GLP-1 nor its receptor is necessary for glycemic improvements after RYGB or VSG (39,40).

Severe postprandial hyperinsulinemic hypoglycemia emerges in a very small minority of patients several years after RYGB. The onset is delayed and bears an uncanny resemblance to the alimentary hypoglycemia reported after surgery for peptic ulcer disease. Reports of larger postmeal GLP-1 and insulin responses in these patients compared with asymptomatic RYGB patients suggest a potential pathogenic role for GLP-1 (41). This concept is supported by findings that exendin(9-39) administration eliminates the abnormally high insulin secretion pattern observed in these individuals and prevents hypoglycemia. Symptomatic patients after RYGB exhibit greater exendin(9-39) responsiveness than asymptomatic patients after RYGB (42). Studies comparing intravenous versus oral glucose administration suggest an exaggerated pancreatic β-cell insulin response after oral but not intravenous stimulation (43). The delayed onset of postprandial hyperinsulinemic hypoglycemia after RYGB and peptic ulcer disease surgery is puzzling and might reflect increased β-cell mass and/or function resulting from heightened GLP-1 action. In rodents, GLP-1 exerts antiapoptotic effects on β-cells (44), and in nondiabetic pigs, RYGB led to an increase in β-cell area and islet number 20 days postsurgery, with increased GLP-1R immunoreactivity (45). Whether GLP-1 or RYGB alters β-cell mass in humans is controversial. Some investigators report that β-cell area is increased in post-RYGB hyperinsulinemic/hypoglycemic patients compared with matched obese nonsurgical control subjects (46,47), whereas others contest this assertion (37,38).

Overall, current evidence suggests that GLP-1 mediates some of the postsurgery glycemic benefits to oral nutrient ingestion. However, other gut-derived factors are likely to contribute. Additional studies are needed to determine whether GLP-1 protects/enhances β-cell mass in the longer-term. Regardless of the relative importance of GLP-1 in bariatric/metabolic surgery, a key point is that even this powerful antidiabetes intervention cannot reverse end-stage β-cell failure. The strongest predictors of diabetes nonremission postsurgery are long disease duration, insulin usage, and low C-peptide levels—all likely proxies for irreversible β-cell death.

ROLES OF THE FOREGUT/REDUCED ANTI-INCRETINS

BPD and RYGB cause exclusion of duodenum and at least part of the jejunum from exposure to ingestion nutrients, together with the rapid delivery of incompletely digested food to the distal bowel. The foregut hypothesis postulates that proximal intestinal exclusion diminishes/eliminates a pathophysiological rise in an unknown anti-incretin signal that normally serves to counteract incretin-mediated insulin secretion and prevent postprandial hypoglycemia. An experimental procedure, DJB, was developed to examine the role of excluding the duodenum and proximal jejunum (similar to RYGB) in the absence of gastric restriction. In Goto-Kakizaki rats, a nonobese T2DM model, DJB improved glycemic control without reducing food intake or body weight (49). Similar observations have been made using obese diabetic Zucker rats (50). DJB redirects and enhances nutrient flow into the midjejunum. These findings led Lam and colleagues to investigate whether increased jejunal nutrient exposure affected glycemic control. They demonstrated that jejunal nutrient sensing was required for the early improvement of glycemia induced by DJB in nonobese rodents with uncontrolled diabetes. Moreover, they identified that DJB-enhanced jejunal-nutrient sensing lowered endogenous glucose production via a gut–brain–liver neurocircuit (18).

The effect of DJB on GLP-1 is controversial. Increased GLP-1 plasma levels and a deterioration of DJB-induced glycemic improvements were reported with administration of exendin(9-39) (51), although other studies report no such changes, implicating duodenal nutrient exclusion per se in improving insulin sensitivity, independent of incretins or insulin (52). Differences in postoperative duration may account for this discrepancy, with GLP-1 changes reported late postsurgery but not acutely. Because VSG improves glucose homeostasis without duodenal exclusion, some have challenged the importance of duodenal exclusion and anti-incretins. However, the mechanisms by which different bariatric/metabolic procedures improve glucose tolerance are likely to vary and cannot be used as evidence to discount a role for duodenal exclusion in regulating glucose tolerance.

INTESTINAL ADAPTATION

RYGB and VSG lead to marked intestinal adaptations that may contribute to improved glucose homeostasis. However,

emerging evidence suggests that major differences exist between these two procedures regarding glucose uptake (53). After RYGB, the alimentary limb undergoes hyperplasia and hypertrophy, together with increased expression of glucose transporters, increased uptake of glucose into intestinal epithelial cells, and reprogramming of intestinal glucose metabolism to support tissue growth and increased bioenergetic demands. The number of cells producing GLP-1 and GIP within the alimentary limb also increases (53). Furthermore, positron emission tomography–computed scanning and biodistribution analysis using 2-deoxy-2-[^{18}F]fluoro-D-glucose in rodents and humans show that the alimentary limb becomes a major site for glucose disposal (53,54). These changes are likely to contribute to improved glycemic control. In contrast, there is no evidence of GI tract hyperplasia after VSG. However, the number and density of cells containing GLP-1 reportedly increase after VSG in rodents. Moreover, VSG reduces intestinal glucose absorption, potentially contributing to improved glucose tolerance (53). These findings yet again highlight that RYGB and VSG improve glucose homeostasis by different—as well as overlapping—mechanisms.

BA, FGF-19, AND THE GUT MICROBIOME

Circulating BA levels increase in humans and rodents after RYGB and VSG, correlating with improved glucose tolerance. Similarly, circulating FGF-19 levels increase after RYGB and VSG, although the time course of these changes and the BA composition details are actively debated. In contrast, neither caloric restriction nor LAGB alters circulating BA or FGF-19 levels (55). The anatomical rearrangements after RYGB lead to delayed mixing of BAs with ingested food and exposure of the ileum to digestate-free chyme, offering a plausible explanation for increased circulating BAs and FGF-19 levels. This notion is supported by the finding that ileal interposition, with attendant increased BA exposure, leads to increased circulating BA levels (56). Although VSG causes rapid gastric emptying, ingested nutrients and BAs mix within the duodenum; thus, mechanisms other than increased BA exposure are involved. In mice post-VSG, increased ileal expression of the apical sodium bile salt transporter is reported, potentially contributing to increased circulating BA levels (57).

Patients with T2DM exhibit reduced circulating BA and FGF-19 levels compared with normoglycemic individuals, regardless of BMI. Furthermore, patients with post-RYGB T2DM remission exhibit higher circulating FGF-19 and BA levels compared with nonremitters (58). These findings imply a link between T2DM/insulin resistance, FGF-19, and BA but do not prove causality. However, catheter-mediated bile diversion to the middistal jejunum in lean and obese rodents leads to increased circulating BAs and improved glucose homeostasis independently of weight loss and food intake (59). BA diversion is associated with reduced hepatic glucose production and increased intestinal gluconeogenesis within gut segments devoid of bile. Administration of BA sequestrants or adding BA back to gut regions with BAs negates the beneficial effects of bile diversion on glucose control, suggesting that BA bioavailability is causal.

Pattou and colleagues, using a mini-pig RYGB model, recently provided further insights into potential mechanisms operating here (60). They showed that intestinal uptake of ingested glucose is blunted in the BA-deprived alimentary limb, despite intact expression of the sodium-glucose cotransporter-1. BA addition restored alimentary limb glucose uptake, an effect abolished by phlorizin, a sodium-glucose cotransporter-1 inhibitor. Given the high concentration of sodium in bile, they examined the effect of adding sodium alone to the alimentary limb (which has low sodium levels post-RYGB) and observed increased glucose uptake. Their findings suggest that BAs modulate glucose homeostasis partly by altering sodium-glucose intestinal cotransport. Reduced alimentary limb intestinal glucose uptake could account for earlier findings of increased gluconeogenesis within the alimentary limb. However, these observations are somewhat at odds with reports from rodents and humans of increased alimentary limb glucose utilization. Methodological issues could underlie these differences; alternatively, circulating glucose, rather than intestinal glucose, might be the source. Another key source of intestinal sodium is gastric sodium bicarbonate. Thus, reduced intestinal sodium after VSG would be anticipated and offers a plausible explanation for reduced intestinal glucose uptake post-VSG. In addition to altering intestinal glucose uptake, enhanced ileal BA exposure leads to increased circulating levels of FGF-19 and GLP-1, with reduced hepatic glucose production and increased tissue uptake of glucose via insulin-dependent and -independent mechanisms.

Caloric restriction, bile diversion, RYGB, and VSG lead to gut microbiome changes, with modulation from an obese bacterial profile, with a high ratio of Firmicutes to Bacteroidetes, to a leaner bacterial profile. Bacteroidetes play a key role in bile acid deconjugation; hence, this change could affect BA composition. A recent longitudinal study found a biphasic increase in total fasting plasma BA levels post-RYGB. The early peak, 1 month postsurgery, was due to bacterially derived secondary BAs such as ursodeoxycholic acid. A later peak 2 years post-RYGB reflected increased primary BAs and the secondary BAs deoxycholic acid and glycodeoxycholic acid. Circulating FGF-19 increased, but not until several months postsurgery after the more rapid metabolic improvements had occurred (61). The early changes in ursodeoxycholic acid and its metabolites may contribute to early improvements in insulin sensitivity after RYGB.

Three lines of evidence suggest a role for the microbiome in contributing to the beneficial effects of bariatric surgery. Firstly, Kaplan and colleagues found that germ-free mice treated with fecal transplants from RYGB-treated mice lost weight, whereas similar recipients given fecal transplants from weight-matched sham-operated mice gained weight. Alterations in microbially produced short-chain fatty acids were proposed as potential mediators (62). Secondly, studies undertaken by Ryan et al., using global FXR knockout (FXRKO) mice, suggest a key role for the BA–FXR–microbiome pathway in mediating the weight-reducing and glycemic effects of VSG. After VSG, circulating BA changes, weight loss, and glycemic improvements were attenuated in global FXRKO mice compared with wild-type mice, together with altered microbiome composition (63). However, whether these microbiome changes relate to metabolic differences or FXR deficiency

per se is unclear. The use of global FXRKO mice makes interpreting these findings difficult due to the phenotype of those animals, which includes increased circulating BAs, altered adaptive thermogenesis, insulin resistance, and resistance to diet-induced obesity (64). Future studies in mice with intestine-specific FXR deletion will help clarify underlying mechanisms. Thirdly, Tremaroli et al. showed that RYGB and VSG led to long-term comparable alterations in the human gut microbiome that were independent of BMI. Fecal transplant from RYGB and VSG patients reduced adiposity in recipient mice (65).

Overall, these studies show that RYGB and VSG increase circulating BA, FGF-19, and GLP-1 levels, also altering intestinal glucose utilization and the gut microbiome. These changes favor improved glucose tolerance and weight loss and are likely to contribute to the antidiabetes effects of RYGB and VSG.

FUTURE PERSPECTIVES

The impressive antidiabetes effects of bariatric/metabolic surgery in T2DM patients impel ongoing efforts to further clarify mechanisms mediating these benefits. This will not be easy, because it is becoming increasingly apparent that surgery engages a constellation of interrelated peripheral and central changes that together improve glycemic control. However, increasing evidence that RYGB and VSG influence glycemic control through differential mechanisms highlights the opportunity to use different GI interventional procedures as tools to gain insights into the glucoregulatory effects of various regions of the GI tract. A further relevant complexity is the diverse underlying biology of patient groups studied; for example, men versus women, insulin-treated T2DM versus newly diagnosed, and class I obesity versus class III, etc. Indeed, the ultimate challenge and opportunity lie in tailoring the most effective therapeutic options to individual patients and identifying the optimum time to intervene.

Acknowledgments. The authors would like to thank Karima Yousseif (University College London) for the illustrations.

Funding. R.L.B. is supported by grants from the Rosetrees Trust and Stoneygate Trust. D.E.C. is supported by National Institute of Diabetes and Digestive and Kidney Diseases grants RO1-DK-103842, RO1-DK-084324, RO1-DK-089528, and U34-DK-107917.

Duality of Interest. D.E.C. is a principal investigator on the Comparison of Surgery vs. Medicine for Indian Diabetes (COSMID) trial, which is funded by Johnson & Johnson, and the Alliance of Randomized Trials of Medicine vs Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D) trial, which is funded by Johnson & Johnson and Covidien, in conjunction with the National Institutes of Health. No other potential conflicts of interest relevant to this article were reported.

References

1. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014;383:1068–1083
2. Rutter GA. Dorothy Hodgkin Lecture 2014. Understanding genes identified by genome-wide association studies for type 2 diabetes. Diabet Med 2014;31:1480–1487
3. Barnes CG. Hypoglycaemia following partial gastrectomy; report of three cases. Lancet 1947;2:536–539
4. Evensen OK. Alimentary hypoglycemia after stomach operations and influence of gastric emptying on glucose tolerance curve. Acta Med Scand 1942;110:143–153
5. Herbst CA, Hughes TA, Gwynne JT, Buckwalter JA. Gastric bariatric operation in insulin-treated adults. Surgery 1984;95:209–214
6. Pories WJ, MacDonald KG Jr, Flickinger EG, et al. Is type II diabetes mellitus (NIDDM) a surgical disease? Ann Surg 1992;215:633–642; discussion 643
7. Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995; 222:339–350; discussion 350–352
8. Inabnet WB 3rd, Winegar DA, Sherif B, Sarr MG. Early outcomes of bariatric surgery in patients with metabolic syndrome: an analysis of the bariatric outcomes longitudinal database. J Am Coll Surg 2012;214:550–556; discussion 556–557
9. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007;132: 2131–2157
10. Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. Ann Surg 2002;236:554–559
11. Salinari S, Debard C, Bertuzzi A, et al. Jejunal proteins secreted by db/db mice or insulin-resistant humans impair the insulin signaling and determine insulin resistance. PLoS One 2013;8:e56258
12. Alfa RW, Park S, Skelly KR, et al. Suppression of insulin production and secretion by a decretin hormone. Cell Metab 2015;21:323–333
13. Penney NC, Kinross J, Newton RC, Purkayastha S. The role of bile acids in reducing the metabolic complications of obesity after bariatric surgery: a systematic review. Int J Obes 2015;39:1565–1574
14. Sayin SI, Wahlström A, Felin J, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metab 2013;17:225–235
15. Fang S, Suh JM, Reilly SM, et al. Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. Nat Med 2015;21:159–165
16. Scarlett JM, Schwartz MW. Gut-brain mechanisms controlling glucose homeostasis. F1000Prime Rep 2015;7:12
17. Wang PY, Caspi L, Lam CK, et al. Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. Nature 2008;452: 1012–1016
18. Breen DM, Rasmussen BA, Kokorovic A, Wang R, Cheung GW, Lam TK. Jejunal nutrient sensing is required for duodenal-jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. Nat Med 2012;18: 950–955
19. Salinari S, Carr RD, Guidone C, et al. Nutrient infusion bypassing duodenum-jejunum improves insulin sensitivity in glucose-tolerant and diabetic obese subjects. Am J Physiol Endocrinol Metab 2013;305:E59–E66
20. Kellum JM, Kuemmerle JF, O'Dorisio TM, et al. Gastrointestinal hormone responses to meals before and after gastric bypass and vertical banded gastroplasty. Ann Surg 1990;211: 763–770; discussion 770–771
21. Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg 2004;239:1–11
22. Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab 2005;288:E447–E453
23. Ramnanan CJ, Edgerton DS, Cherrington AD. Evidence against a physiologic role for acute changes in CNS insulin action in the rapid regulation of hepatic glucose production. Cell Metab 2012;15:656–664
24. Laferrère B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab 2008;93:2479–2485
25. Plum L, Ahmed L, Febres G, et al. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. Obesity (Silver Spring) 2011;19:2149–2157
26. Jackness C, Karmally W, Febres G, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β-cell function in type 2 diabetic patients. Diabetes 2013;62:3027–3032
27. Lingvay I, Guth E, Islam A, Livingston E. Rapid improvement in diabetes after gastric bypass surgery: is it the diet or surgery? Diabetes Care 2013;36:2741–2747
28. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. Diabet Med 2013;30:267–275
29. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011;54:2506–2514
30. Steven S, Hollingsworth KG, Small PK, et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. Diabetes Care 2016;39:158–165
31. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal

adaptations to weight loss. N Engl J Med 2011; 365:1597–1604
32. Manning S, Pucci A, Batterham RL. Roux-en-Y gastric bypass: effects on feeding behavior and underlying mechanisms. J Clin Invest 2015;125: 939–948
33. Martinussen C, Bojsen-Møller KN, Dirksen C, et al. Immediate enhancement of first-phase insulin secretion and unchanged glucose effectiveness in patients with type 2 diabetes after Roux-en-Y gastric bypass. Am J Physiol Endocrinol Metab 2015;308:E535–E544
34. Manning S, Pucci A, Batterham RL. GLP-1: a mediator of the beneficial metabolic effects of bariatric surgery? Physiology (Bethesda) 2015; 30:50–62
35. Ramzy AR, Nausheen S, Chelikani PK. Ileal transposition surgery produces ileal length-dependent changes in food intake, body weight, gut hormones and glucose metabolism in rats. Int J Obes 2014;38:379–387
36. Yousseif A, Emmanuel J, Karra E, et al. Differential effects of laparoscopic sleeve gastrectomy and laparoscopic gastric bypass on appetite, circulating acyl-ghrelin, peptide YY3-36 and active GLP-1 levels in non-diabetic humans. Obes Surg 2014;24:241–252
37. Dutia R, Brakoniecki K, Bunker P, et al. Limited recovery of β-cell function after gastric bypass despite clinical diabetes remission. Diabetes 2014;63:1214–1223
38. Chambers AP, Jessen L, Ryan KK, et al. Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. Gastroenterology 2011;141:950–958
39. Chambers AP, Smith EP, Begg DP, et al. Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. Am J Physiol Endocrinol Metab 2014;306:E424–E432
40. Mokadem M, Zechner JF, Margolskee RF, Drucker DJ, Aguirre V. Effects of Roux-en-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. Mol Metab 2013;3:191–201
41. Goldfine AB, Mun EC, Devine E, et al Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. J Clin Endocrinol Metab 2007;92:4678–4685
42. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. Gastroenterology 2014;146:669–680.e2
43. Patti ME, Li P, Goldfine AB. Insulin response to oral stimuli and glucose effectiveness increased in neuroglycopenia following gastric bypass. Obesity (Silver Spring) 2015;23: 798–807
44. Chambers AP, Wilson-Perez HE, McGrath S, et al. Effect of vertical sleeve gastrectomy on food selection and satiation in rats. Am J Physiol Endocrinol Metab 2012;303:E1076–E1084
45. Lindqvist A, Spégel P, Ekelund M, et al. Gastric bypass improves β-cell function and increases β-cell mass in a porcine model. Diabetes 2014;63:1665–1671
46. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med 2005;353:249–254
47. Patti ME, McMahon G, Mun EC, et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia 2005;48:2236–2240
48. Meier JJ, Butler AE, Galasso R, Butler PC. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. Diabetes Care 2006;29:1554–1559
49. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg 2006;244:741–749
50. Rubino F, Zizzari P, Tomasetto C, et al. The role of the small bowel in the regulation of circulating ghrelin levels and food intake in the obese Zucker rat. Endocrinology 2005;146: 1745–1751
51. Kindel TL, Yoder SM, Seeley RJ, D'Alessio DA, Tso P. Duodenal-jejunal exclusion improves glucose tolerance in the diabetic, Goto-Kakizaki rat by a GLP-1 receptor-mediated mechanism. J Gastrointest Surg 2009;13:1762–1772
52. Salinari S, le Roux CW, Bertuzzi A, Rubino F, Mingrone G. Duodenal-jejunal bypass and jejunectomy improve insulin sensitivity in Goto-Kakizaki diabetic rats without changes in incretins or insulin secretion. Diabetes 2014;63: 1069–1078
53. Cavin JB, Couvelard A, Lebtahi R, et al. Differences in alimentary glucose absorption and intestinal disposal of blood glucose after Roux-en-Y gastric bypass vs sleeve gastrectomy. Gastroenterology 2016;150:454–464.e9
54. Saeidi N, Meoli L, Nestoridi E, et al. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. Science 2013;341:406–410
55. Sachdev S, Wang Q, Billington C, et al. FGF 19 and bile acids increase following Roux-en-Y gastric bypass but not after medical management in patients with type 2 diabetes. Obes Surg 2015
56. Kohli R, Kirby M, Setchell KD, et al. Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity-related comorbidities. Am J Physiol Gastrointest Liver Physiol 2010;299:G652–G660
57. Ding L, Yang L, Wang Z, Huang W. Bile acid nuclear receptor FXR and digestive system diseases. Acta Pharm Sin B 2015;5:135–144
58. Gerhard GS, Styer AM, Wood GC, et al. A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. Diabetes Care 2013;36:1859–1864
59. Kohli R, Setchell KD, Kirby M, et al. A surgical model in male obese rats uncovers protective effects of bile acids post-bariatric surgery. Endocrinology 2013;154:2341–2351
60. Baud G, Daoudi M, Hubert T, et al. Bile diversion in Roux-en-Y gastric bypass modulates sodium-dependent glucose intestinal uptake. Cell Metab 2016;23:547–553
61. Albaugh VL, Flynn CR, Cai S, Xiao Y, Tamboli RA, Abumrad NN. Early increases in bile acids post Roux-en-Y gastric bypass are driven by insulin-sensitizing, secondary bile acids. J Clin Endocrinol Metab 2015;100:E1225–E1233
62. Liou AP, Paziuk M, Luevano JM Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med 2013;5:178ra41
63. Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature 2014;509:183–188
64. Kuipers F, Groen AK. FXR: the key to benefits in bariatric surgery? Nat Med 2014;20:337–338
65. Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. Cell Metab 2015;22: 228–238