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Mechanisms of weight loss and improved metabolism following bariatric surgery

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Abstract

Bariatric surgery is increasingly recognized as one of the most effective interventions to help patients achieve significant and sustained weight loss, as well as improved metabolic and overall health. Unfortunately, the cellular and physiological mechanisms by which bariatric surgery achieves weight loss have not been fully elucidated yet are critical to understand the central role of the intestinal tract in whole-body metabolism and to develop novel strategies for the treatment of obesity. In this review, we provide an overview of potential mechanisms contributing to weight loss, including effects on regulation of energy balance and both central and peripheral nervous system regulation of appetite and metabolism. Moreover, we highlight the importance of the gastrointestinal tract, including alterations in bile acid physiology, secretion of intestinally derived hormones, and the microbiome, as a potent mediator of improved metabolism in postbariatric patients.

Keywords

bariatric surgery; obesity; Roux-en-Y gastric bypass; sleeve gastrectomy; adjustable gastric band

Introduction

The global prevalence of overweight (body mass index (BMI) 25–30 kg/m²) or obesity (> 30 kg/m²) in adults is estimated to be 2.1 billion people and has been rising in both developed and developing countries.¹ This is a particularly important public health concern in the United States; the Centers for Disease Control estimated that the prevalence of obesity among adults was 37.7% in 2014.² The health and economic impact of obesity cannot be overstated, with increased mortality³ and comorbidities, including coronary artery disease,^{3–5} hypertension,⁶ hyperlipidemia,⁷ type 2 diabetes mellitus (T2D), sleep apnea,⁸ osteoarthritis,^{9,10} and many forms of cancer.¹¹ The associated costs of medical care for obesity-related illnesses in the United States are estimated at \$147–185 billion per year.^{12,13}

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Competing interests

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Bariatric surgery, also known as metabolic surgery, is increasingly recognized as one of the most effective interventions for obesity and associated conditions, helping patients to achieve significant and sustainable weight loss, as well as improved overall health. The number of procedures in the United States has increased by 24% since 2011, reaching a total of more than 190,000 in 2015.^{14,15} Despite increasing utilization of bariatric surgeries, the underlying mechanisms are not well understood. In this review, we highlight bariatric procedures and potential mechanisms contributing to weight loss and improved whole-body metabolism (Table 1).

Types of bariatric surgery

Surgical approaches to treat obesity were first reported in Sweden in 1952.¹⁶ Procedures have evolved substantially over time and now include three dominant versions performed in the United States (Fig. 1). Roux-en-Y gastric bypass (RYGB), often referred to as gastric bypass, has traditionally been considered the gold standard bariatric procedure (Fig. 1B). RYGB accounted for 26.8% of bariatric procedures in the United States in 2014¹⁴ and for 38%, 60%, and 25% of surgeries in Europe, Latin/South America and Asia/Pacific, respectively, in 2013.¹⁷ In RYGB, a small 15- to 30-mL pouch is created from the proximal stomach; this pouch is connected to a loop of jejunum, creating a gastrojejunostomy. The remainder of the stomach and proximal small bowel is left intact and re-anastomosed 80–120 cm distal to the gastrojejunostomy, thus remaining isolated from digestive flow.¹⁸ Vertical sleeve gastrectomy (VSG) is increasingly performed, accounting for 54% of bariatric procedures in the United States in 2015^{15,19} (Fig. 1C). VSG consists of removing ~80% of the stomach along the greater curvature, creating a tube-like stomach remnant, with the rest of the intestine intact. Finally, in laparoscopic adjustable gastric banding (LAGB), which accounted for only 6% of procedures in the United States in 2015,¹⁵ an inflatable band is placed around the upper portion of the stomach, creating a small gastric pouch proximal to the band (Fig. 1D). The band can be inflated or deflated via an external port as needed to achieve weight loss goals, while minimizing gastrointestinal symptoms. Other procedures, such as biliopancreatic diversion and duodenal switch, are not typically performed in the United States.

Comparative efficacy of bariatric surgery versus medical therapy for obesity

Multiple clinical trials have demonstrated superior efficacy and sustainability of weight loss and resolution of obesity-related comorbidities following bariatric surgery compared with intensive medical and lifestyle interventions.^{20–23} For example, one randomized clinical trial (RCT) demonstrated superior weight loss at 3 years after RYGB, with a mean reduction in body weight of 25%, as compared with 15% after LAGB and 6% with lifestyle intervention.²⁴ Moreover, results from recent RCTs in patients with type 2 diabetes have also demonstrated superiority of weight loss and remission of diabetes after surgery as compared with medical interventions.^{20–23} Similar results have been demonstrated in other RCTs and retrospective uncontrolled observational series.^{25–27}

While these data underscore the robust and sustained impact of bariatric surgery, the underlying mechanisms contributing to weight loss have not been fully elucidated. Understanding these mechanisms is a hot topic in research, as this information could lead to more individualized choice of surgical procedure, refined surgical techniques, or development of nonsurgical interventions to induce sustainable weight loss.

Macronutrient and micronutrient absorption and gut enteroplasticity

Macronutrients

Historically, the induction of caloric malabsorption by surgical alteration of gastrointestinal anatomy was viewed as the likely mechanism by which surgery could promote weight loss²⁸ and result in associated macro- and micronutrient deficiencies. However, RYGB does not change intestinal length or orocecal transit time.²⁹ Indeed, carbohydrate malabsorption has not been detected.³⁰ By contrast, fecal fat content is increased after RYGB, indicating fat malabsorption.^{29,31,32} In the less routinely performed duodenal switch or biliopancreatic diversion procedures, fat malabsorption occurs to a greater extent.²⁹ Nevertheless, one study found that the reduction in energy absorption averaged only 124–172 kcal/day after RYGB, in contrast to reductions in caloric intake of 1418–2062 kcal/day at 5–14 months after surgery.³² Thus, malabsorption accounts for < 10% of observed weight loss,^{29,32} indicating that global caloric malabsorption is not likely the dominant mechanism.

Enterocytes lining the intestinal lumen have rapid turnover and are highly plastic, adapting their structure and function in response to many stressors, such as malabsorption, aging, diabetes, and even fasting.^{33,34} Surgically induced changes in gut structure, such as resection or transposition of the proximal small bowel, can also lead to changes in intestinal morphology, including villus height, crypt depth, mucosal surface area, and intestinal weight; these, in turn, could affect nutrient absorption.³⁵ Resection of three-fourths of the proximal small bowel in rats increases villus height, intestinal length, and ileal glucose uptake, despite no change in expression of glucose transporters.³⁶ Bariatric surgery also modulates glucose uptake by enterocytes. Fluorodeoxyglucose uptake, assessed using PET scanning, is increased in the Roux limb in rodents with a history of RYGB,³⁷ potentially owing to GLUT1-mediated uptake of glucose from the basolateral surface of enterocytes. In turn, increases in GLUT1 protein are accompanied by upregulation of anabolic protein and nucleotide synthesis pathways in the Roux limb.³⁷ Similar increases in intestinal glucose uptake have been observed in human studies of postbariatric patients undergoing PET scanning.^{38,39} Uptake of ingested (luminal) glucose by SGLT1-dependent mechanisms has a distinct pattern and appears to be restricted to the common limb, where meal contents merge with biliopancreatic secretions.⁴⁰ Whether altered intestinal glucose absorption from either the lumen or basolateral surface of enterocytes is sufficient to impact secretion of hormones, whole-body glucose utilization, or weight loss remains uncertain.

Micronutrients

Micronutrient deficiency occurs commonly after bariatric surgery. For example, iron deficiency occurs in half of postbariatric patients.⁴¹ Vitamin B₁₂ deficiency often occurs after RYGB,^{42,43} a likely result of achlorhydria, decreased intrinsic factor, and impaired

release of vitamin B₁₂ from food. Additional deficiencies commonly observed include vitamin D, calcium, and folate.^{44,45} These micronutrient deficiencies are important to recognize during postoperative clinical care, but are not likely to contribute directly to weight loss.

Changes in food intake and macronutrient preference

Multiple studies have demonstrated that caloric intake is reduced following bariatric surgery.^{46–48} These dietary modifications appear to be due to more than just alterations in anatomy, with major contributions from substantial changes in food preference and taste after surgery.

Total calories

The largest reduction in caloric consumption occurs immediately following surgery. For example, one prospective study of 41 individuals with mean BMI of 44.6 ± 6.3 kg/m² in Brazil found reduction in calorie intake from 3000 kcal/day preoperatively to 1000 kcal/day six months after RYGB.⁴⁹ Other studies found similar reductions in caloric intake, with daily total calories of 1000–1800 kcal/day within the first year.^{46–48} Caloric intake may gradually return to presurgical levels by one year postoperatively,⁵⁰ but reduced intake may be sustained as long as 4 years.⁵¹

Protein, fat, and carbohydrate intake

Quantitative analysis of dietary changes within the first 2 years following RYGB has revealed significant heterogeneity. For example, one study demonstrated increased proportion of protein consumption but unchanged fat and carbohydrate intake.⁵² By contrast, other studies revealed preference for low-fat foods (< 30% calories from fat)⁵³ or reduced consumption of unhealthy foods, but no significant difference in the proportion of consumed carbohydrate, protein, or fat.⁴⁹ Whether these differences are related to cultural differences or trained dieting behavior remains uncertain. However, it is notable that differences in macronutrient proportions have not been observed in patients who have had solely restrictive procedures, such as vertical banded gastroplasty,^{54,55} indicating that RYGB is superior to restrictive procedures in altering eating behavior.

Change in specific food preferences, taste, and smell

Changes in preference for certain types of foods, potentially influenced by changes in taste acuity or olfaction, may also affect overall caloric consumption and thus contribute to weight loss after bariatric surgery. For example, the intake of high-calorie beverages or foods, such as ice cream, is significantly decreased following RYGB.⁵² Functional magnetic resonance imaging (fMRI) reveals decreased brain hedonic responses to high-calorie foods in post-RYGB as compared with post-LAGB patients.^{56–58} In addition, gastrointestinal symptoms linked to lactose intolerance, altered taste, or dumping syndrome may contribute to food aversions.⁵² Changes in food preference are also procedure specific, with preference for unprocessed vegetables and fruits over high-fat foods in RYGB; these patterns were attributed to symptoms related to the dumping syndrome.⁵⁹

The interplay among taste and olfactory signals, food selection, and overall energy intake⁶⁰ may also be affected by bariatric surgery. One report noted that more than half of patients who had either RYGB or VSG had a perceived change in taste and an increase in food aversions.⁶¹ However, only 44% of post-RYGB and 15% of post-VSG patients perceive a change in smell by 1–2 years after surgery.⁶¹ Given the small effect in both groups, changes in eating behavior are unlikely to be fully explained by such olfactory changes.⁶¹

Whether bariatric surgery has an effect on taste remains uncertain. Some studies indicate that bariatric surgery may have subtle effects on taste detection thresholds and sweetness acceptability.^{61,62} One study used a modification of the Henkin forced-choice three-stimulus technique,⁶³ in which subjects are asked to rate the intensity of sweet (sucrose), salty (NaCl), sour (HCl), or bitter (urea) tastes.⁶⁴ Post-RYGB patients had an increase in taste acuity for bitter and sour stimuli and a trend towards increased sensitivity to detect salt and sweet tastes as compared with their presurgical baseline.⁶³ In another study, post-RYGB patients demonstrated a higher sour taste threshold, and thus lower sour taste sensitivity, compared with patients who underwent VSG.⁶² By contrast, Makaronidis *et al.* found no evidence of altered sensitivity thresholds for sweetness, bitterness, or saltiness after RYGB compared with VSG.⁶¹ The etiology of taste changes, when detected, is uncertain; they do not appear to be related to a deficiency of zinc, an important taste effector.⁶⁵

Increased sensitivity to detect sweetness may be affected by increases in GLP-1 levels after RYGB and VSG, as both GLP-1 and GLP-1 receptors are expressed in taste buds and may thus modulate the gustatory apparatus.⁶⁶ In addition to GLP-1 receptors, receptors for insulin, leptin, PYY, and ghrelin have been identified on taste buds and olfactory neurons, and there is emerging evidence that these hormones may modulate taste.^{60,67,68} It remains uncertain whether the variable and modest changes in taste sensitivity modify dietary caloric intake and thereby contribute to weight reduction. Nevertheless, changes in food preference after bariatric surgery may be influenced by changes in olfaction and taste acuity; these may reduce calories consumed and contribute to weight loss in some patients.

Appetite and reward signaling pathways

As early as the late 1970s, it was found that RYGB alters feeding behavior, with both increased satiety and reduced hunger.^{51,69–72} Altered taste and smell and food aversions, as noted above, may also affect reward signaling mechanisms.^{53,73} Moreover, intestinally derived hormones changed after RYGB may contribute to regulation of appetite and reward signaling in the brain.

Hypothalamic signaling

The hypothalamus is the master regulator of food intake via a complex system of anorexic and orexigenic neuronal signaling. Pro-opiomelanocortin (POMC)-derived peptides act via melanocortin receptor 4 (MC4R) to reduce food intake and increase energy expenditure. Another group of neurons produces agouti-related protein (AgRP), which increases food intake. In turn, production of these neuropeptides in the arcuate nucleus of the hypothalamus is under the control of nutrients and circulating gut-derived peptide hormones.⁷⁴

Diet-induced weight loss and bariatric surgery may have distinct effects on these hypothalamic neuropeptides. VSG in rats did not change AgRP expression as compared with sham-operated animals, while pair-fed rats demonstrated an increase in AgRP expression that was attributed to longer fasting periods inherent to experimental pair feeding. Moreover, VSG modestly improved the anorectic action of leptin, with magnitude similar to calorie-restricted controls; such neuropeptide expression changes paralleled reductions in body weight.⁷⁵ In mice, signaling via MC4R is critical for surgical weight loss.⁷⁶ However, humans with a heterozygous mutation in the MC4R gene do lose weight after surgery, suggesting that MC4R-related signaling may not be essential for bariatric surgery-induced weight loss in humans.⁷⁶

Peripheral nervous system

The peripheral nervous system has also been directly implicated in altering food intake. Afferent vagal nerve fibers in the stomach and duodenum are sensitive to mechanical stretch related to food ingestion^{77,78} and also integrate additional visceral sensory information with hormonal and metabolic signals and neuronal inputs from the brain stem.⁷⁹ Vagal fibers to the gastric pouch remain largely intact after RYGB, and these may signal satiety to the brain.⁸⁰ After vagotomy, signals from gut hormones, including ghrelin, are impaired.⁸¹ Furthermore, celiac branch vagotomy performed at the time of RYGB in rats yielded lower degrees of weight loss than RYGB alone. These data suggest that vagal afferent signals may contribute to RYGB-induced weight loss.⁸² Tracer studies in rats also show that RYGB reduces vagal afferent nerve density and activates microglia in the tract of the solitary nucleus, and thus may modify nerve signaling between the gastrointestinal system and the brain.⁸³

Gut hormones

Gut hormones play a crucial role in regulating appetite, satiety, food intake, systemic metabolism, and insulin secretion.⁸⁴ Some forms of bariatric surgery increase the secretion of multiple intestinally derived peptides, including GLP-1, PYY, and FGF-19, but decrease the secretion of others, such as GIP and ghrelin.

PYY

Peptide YY (PYY) is secreted from L cells of the distal small intestine and colon, and levels are increased in the postprandial state.⁸⁵ Exogenous administration of PYY reduces food intake.⁸⁶ The effects of PYY are thought to be mediated through central appetite-regulating circuits and food reward regions in the corticolimbic and higher cortical areas, as well as homeostatic brain regions, such as the hypothalamus and brainstem. In turn, these regions of the brain integrate hormonal, nutrient, and neural input and orchestrate appropriate responses.⁸⁷

After RYGB, plasma levels of PYY increase modestly (~ 20%) in the fasting state⁸⁸ and by 3.5-fold in the postprandial state.⁸⁹ Similarly, postprandial levels of PYY increase 1 year following VSG.⁹⁰ By contrast, PYY levels increase minimally following LAGB.⁸⁹ Animal studies support a prominent role for PYY in mediating bariatric weight loss, as postsurgical

weight loss is lower in PYY gene knockout as compared with wild-type mice,⁹¹ and infusion of anti-PYY antibodies increases food intake in post-bypass rats.⁹² Thus, enhanced PYY secretion may contribute to weight loss after RYGB.

GLP-1

GLP-1 is another L cell–derived hormone that is increased in both the fasting and postprandial states as early as 2 days after RYGB;⁹³ such increases in GLP-1 are sustained up to 10 years post-RYGB.⁹⁴ Postprandial levels of GLP-1 also increase after VSG as much as 1.7 fold and as early as 6 weeks postoperatively; however, fasting levels do not change.⁹⁵ By contrast, GLP-1 levels are not altered after LAGB.^{89,96}

GLP-1 has received major attention as a potential hormonal mediator of the beneficial metabolic effects of bariatric surgery, as it increases glucose-dependent insulin secretion, and GLP-1 analogues are highly effective therapeutics for human T2D and obesity. However, it remains uncertain to what extent this peptide is responsible for the beneficial effects of bariatric surgery. In both post-RYGB and sham-operated rats, central infusion of the GLP-1 receptor antagonist exendin-9 increases food intake and weight gain, indicating the potent effect of the hormone. However, RYGB-like surgery remains effective in GLP-1R–deficient mice, with weight loss and food intake similar to wild-type mice.⁹⁷ Thus, it is likely that multiple gut hormone responses acting in concert are required to increase postprandial satiety and systemic metabolism.⁹⁷

Recently, functional MRI studies have provided support for the complementary role of PYY and GLP-1 in reducing appetite and food intake in humans. Administration of both PYY(3–36) and GLP-1(7–36 amide) after a standardized breakfast reduced both brain activity, as observed by fMRI, and food intake during a subsequent *ad libitum* buffet compared with placebo.⁹⁸

GIP

Glucose-dependent insulintropic polypeptide (GIP) is an incretin peptide hormone secreted by K cells in the proximal small intestine.⁹⁹ While GIP was previously known as gastric inhibitory peptide, it actually has minimal impact on gastric motility.¹⁰⁰ GIP signaling increases glucose-dependent insulin secretion, postprandial glucagon secretion, and intestinal glucose absorption via increased GLUT-1 expression. Similarly, GIP action in adipose tissue promotes storage, with increased glucose uptake, conversion of glucose to fatty acids (lipogenesis), and activation of lipoprotein lipase.⁹⁹

Some studies demonstrate reductions in fasting GIP after RYGB as early as 2 weeks postoperatively in patients with diabetes^{101,102} but not in individuals without diabetes.¹⁰¹ Postprandial GIP levels were also reduced after RYGB.¹⁰³ By contrast, fasting GIP levels do not change after LAGB⁹⁶ and may even be increased in the postprandial state as compared with post-RYGB patients.¹⁰⁴ Sleeve gastrectomy has no impact on fasting GIP levels.¹⁰⁵

Ghrelin and other gut hormones

The orexigenic hormone ghrelin, produced in oxyntic glands in the gastric fundus, also regulates the homeostatic and reward centers that control appetite and eventually energy intake and may enhance the hedonic response to food.¹⁰⁶ Ghrelin concentrations increase in the fasted state and decrease in the postprandial state. Ghrelin levels are markedly suppressed following bariatric surgery in some¹⁰⁷ but not all studies.^{108–110} At least two studies have demonstrated marked increases in ghrelin levels in the postprandial state following LAGB.^{89,111}

Other gut hormones also affect feeding behavior. Like GLP-1 and PYY, the proglucagon–derived peptide oxyntomodulin has anorectic effects, is increased after glucose load, and is increased early after RYGB, indicating that this is a weight-independent response.^{112,113} However, it is not clear to what extent this hormone regulates appetite and food intake postbariatric surgery. Additional gut hormones, such as ileal-derived fibroblast growth factor-19 (FGF-19, discussed below) may also contribute to weight loss and changes in metabolism following bariatric surgery.

The gut microbiota and microbiome

The average human gut hosts trillions of microorganisms,¹¹⁴ which interact with and affect the metabolic and immunologic systems of their human hosts.¹¹⁵ In turn, the diversity of the microbiota and their function is affected by host genetics and environmental factors, including diet, antibiotic exposure, sleep patterns, and developmental factors.¹¹⁵

Diet composition, independent of weight, can modulate the microbiome. For instance, high intake of protein and animal-derived fats increases the proportion of hydrogen sulfide–producing bacteria after as little as 1 day of exposure.¹¹⁶ Additionally, diets with a high simple sugar content but a paucity of microbe-accessible carbohydrates decrease the biodiversity of the microbiome; this effect appears to be compounded over generations.¹¹⁷

Several studies have demonstrated differences in the microbiome composition of obese, overweight, and lean individuals.^{118–120} Obesity is associated with a relative increase in prevalence of *Ruminococcus* (Firmicutes) and Bacteroidetes, including *Bacteroides* and *Prevotella*,¹²¹ as well as reductions in the phylum Actinobacter, compared with nonobese individuals. Interestingly, the relative abundance of the Verrucomicrobia genus *Akkermansia*, which uses mucin as a carbon source, is inversely correlated with body weight.¹²² The significance of the relative proportions of different species remains an area of active investigation.

While the significance of these differences is still incompletely understood, transplantation of gut bacteria from obese mice to normal-weight germ-free mice results in increased adiposity in the recipients.¹²³ Conversely, fecal transplant from lean human donors to recipient patients with metabolic syndrome led to improvements in insulin sensitivity, paralleling changes in the composition of their microbiota as compared with self-transplantation.¹²⁴ Moreover, transplantation of *Akkermansia muciniphila* into high-fat diet–fed mice improves insulin sensitivity and increases GLP-1 secretion.¹²⁵

While the specific mechanisms responsible for these findings remain uncertain, several mechanisms have been proposed. Microbiota may influence host energy and nutrient metabolism via transcriptional regulation, promoting increased fat storage in adipose tissue,¹²⁶ and by processing indigestible luminal polysaccharides into short chain fatty acids, which can then be absorbed by the host.^{120,121,127,128}

Not surprisingly, bariatric surgery induces profound changes in the microbiome, likely a result of dietary, environmental, systemic, and anatomical changes that accompany bariatric surgery. In rodents, changes in the microbiome can be detected as early as 1 week after RYGB as compared with sham controls,¹²⁹ with decreases in the ratio of Firmicutes to Bacteroidetes and increases in Gammaproteobacteria (*Escherichia coli*), Bacteroidales, Enterobacteriales, and Verrucomicrobia. Similar patterns have been observed in humans following RYGB.^{130–132} Interestingly, *A. muciniphila* increases in response to RYGB.^{122,125} The specific mechanisms responsible for these postoperative changes in the microbiome remain unknown, but could include the impact of perioperative antibiotics, dietary changes, intestinal remodeling after surgery, and weight loss itself.¹³³

Bile acid adaptations after bariatric surgery

Bile acids have long been recognized as important components of bile and mediators of intestinal absorption of lipophilic nutrients. More recently, bile acids are increasingly recognized as mediators of systemic metabolism, serving as ligands for the nuclear receptor farnesoid X receptor (FXR) and the cell surface receptor G protein–coupled bile acid receptor 1 (TGR5). Bile acid supplementation in rodents can reduce weight gain,¹³⁴ and plasma levels of bile acids in the postprandial state are inversely related with body fat mass.¹³⁵ While the effects of bile acids can be observed in multiple organs, bile acids exert particularly interesting effects in the gut lumen, where they can modulate enteroendocrine cell production of critical incretin hormones, such as GLP-1.¹³⁶ Bile acids also directly influence the microbiome through antimicrobial properties of conjugated bile species¹³⁷ and may signal indirectly through activation of ileal nuclear receptor FXR and its downstream products, including ANG1, iNOS, IL-18, and FGF-19.¹³⁸

Forms of bariatric surgery that alter the alimentary route lead to increases in plasma levels of both primary and secondary bile acids.^{139–143} For example, both RYGB and biliopancreatic diversion increase fasting and postprandial bile acids by 2- to 3-fold, with parallel alterations in composition.^{139,140,143} Similar but more modest increases in both fasting and postprandial bile acids are observed after VSG.¹⁴⁴ By contrast, LAGB is not associated with alterations in bile.¹⁴³

Mechanisms responsible for increases in circulating bile acids and altered composition after bariatric surgery remain uncertain, but could include increased hepatic synthesis or altered enterohepatic recirculation of bile. In the case of RYGB, bacterial overgrowth may occur in the biliopancreatic limb (no longer experiencing alimentary flow); altered bacterial modification of bile acids may generate secondary bile acid species¹⁴⁵ with differing affinity for FXR or TGR5 and thus different metabolic effects. Bile acids can also increase circulating levels of the peptide hormone FGF-19 in the postprandial state via activation of

FXR in the ileum. This is of potential mechanistic interest as FGF-19 plays an important role in regulating bile acid synthesis,¹⁴⁶ as well as glucose and lipid metabolism. Indeed, FGF-19 administration to mice fed a high-fat diet improves glucose tolerance, reduces weight gain, and increases metabolic rate.¹⁴⁷ Ryan *et al.* demonstrated that FXR gene knockout mice regained weight lost after VSG and did not have comparable improvements in fasting blood glucose and glucose tolerance as compared to their wild-type controls.¹⁴⁸ Whole-body FXR gene knockout mice are also resistant to dietary obesity; the potential role for alterations in FGF-15 levels (mouse ortholog of human FGF-19) remains unknown.¹⁴⁸ Similarly, whether FXR signaling and/or FGF-19 contributes to improvements in body weight and glycemia after bariatric surgery in humans is uncertain at present.

Interestingly, re-routing bile in the intestine to the distal small bowel by transposing the common bile duct to the ileum results in impressive improvements in metabolism in mice.¹⁴⁹ These include improved body weight, glucose metabolism, and hepatic steatosis, reduced free fatty acids and triglycerides, and increases in plasma bile acids similar to those seen after RYGB. This was associated with increases in intestinal but not hepatic FXR–FGF-15 signaling.¹⁴⁹ Together, this supports the hypothesis that changes in delivery of bile acids to the distal small bowel and bile acid signaling contribute mechanistically to weight loss after some forms of bariatric surgery.

Conclusions

Bariatric surgery is increasingly recognized as one of the most effective interventions to help patients achieve significant and sustainable weight loss, as well as improved overall health. The potential mechanisms by which bariatric surgery achieve weight loss are diverse and have not been fully elucidated. Identifying these mechanisms is of pivotal importance not to only increase our understanding of the role of the intestinal tract in whole-body metabolism but also to develop less-invasive strategies to mimic the benefits of bariatric surgery.

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Figure 1.

Normal and postbariatric surgery anatomy of the intestinal tract. (A) Normal, presurgical anatomy, (B) Roux-en-Y gastric bypass, (C) vertical sleeve gastrectomy, and (D) laparoscopic adjustable gastric banding.

Table 1

Physiologic and behavioral measures affected by the three major forms of bariatric surgery.

	RYGB	VSG	LAGB
CENTRAL AND PERIPHERAL NERVOUS SYSTEM			
Agouti-related protein (AgRP) signaling		↑	
Central anorexic leptin signaling		↑	
Hedonistic response to high calorie food	↓		↔
Afferent vagal nerve density	↓		
ENERGY BALANCE			
Calories consumed	↓	↓	↓
Diet content	↑ Protein and ↓ fat or ↔		↔
Food aversions	↑ (Sweet, high calorie beverages)	↑	
Food preference	↑ Unprocessed fruits and vegetables		↔
Diet content	↑ Protein. ↓ fat		
Perceived change in smell of food	↑↑	↑	
Sour taste detection	↓	↑	
Sweet & bitter taste detection acuity	↑	↔	
Malabsorption (fat)	↑		
Intestinal glucose uptake	↑		
BILE, MICROBIOTA, INTESTINAL HORMONES			
Bile acids	↑↑ Fasting. ↑↑ Post-prandial	↑ Fasting. ↑ post-prandial	↔
Change in gut microbiome	Yes	Yes	
FGF-19	↑↑	↑	
GLP-1	↑ Fasting. ↑↑ Post-prandial	↔ Fasting. ↑ post-prandial	↔
GIP	↔ or ↓ Fasting. ↓ post-prandial	↔ Fasting	↔ Fasting & post-prandia
Ghrelin	↓↔	↓↔	↑↔
Oxyntomodulin	↑		
PYY	↑ Fasting. ↑↑ Post-prandial	↑ Fasting. ↑↑ post-prandial	↑↔

Note: Data are derived from both human and animal studies. ↑ or ↑↑, increase or greater increase; ↓, decrease; ↔, no change; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy; LAGB, laparoscopic adjustable gastric banding.