Mechanisms of Action of Bariatric Surgical Procedures

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Abstract

Bariatric surgery can effectively induce durable weight loss and can reduce the risk of obesity-associated complications, including type 2 diabetes mellitus (T2DM). Bariatric procedures fundamentally alter physiology, and in those with diabetes, bariatric surgery can affect insulin sensitivity and insulin secretion, resulting in remission of diabetes in many recipients. The action of each procedure differs, and the mechanisms by which each procedure produces weight loss and alters physiological mechanisms, such as glucose homeostasis, are multiple and often integrated. The known mechanisms include gut hormone mediated changes affecting appetite, insulin dynamics, food preferences, and energy expenditure. In this review, we outline the current knowledge on the putative mechanisms of weight loss and glucose homeostasis after the most commonly performed bariatric operations.

Keywords

Appetite • Energy expenditure • Stomach size • Malabsorption • Bariatric surgery • Mechanisms • Diabetes mellitus • Obesity • Metabolic surgery

54.1 Introduction

Bariatric surgery effectively reduces body weight, and is the only intervention that maintains weight loss in the long-term. In the Swedish Obese Subjects study, a cohort study of obese patients with a body mass index (BMI) >34 kg/m^2 and a follow-up of more than 20 years, the surgical group achieved up to a 23 % reduction in total body weight as compared to patients receiving conventional non-surgical treatment [1]. Bariatric surgery is also an effective treatment for obesity-associated comorbidities such as type 2 diabetes mellitus (T2DM). Randomized controlled trials have demonstrated that in obese patients with T2DM, bariatric surgery results in better glycemic control than intensive medical therapy alone [2–4].

Previously, bariatric surgery was considered to produce these effects simply by restricting meal size by altering stomach volume, and by macronutrient malabsorption. However, it is now recognized that the effects of bariatric surgery include changes in gut hormones favoring improved insulin dynamics, reduced hunger, increased satiety, and increased energy expenditure [5]. The main hormones that are implicated originate from the endocrine L-cell in the gut and include glucagon-like-peptide 1 (GLP-1), oxyntomodulin (OXM), and peptide YY (PYY). Other hormones such as ghrelin have also been identified as having a role in the postoperative changes in appetite and insulin secretion.

GLP-1, OXM and PYY are synthesized by the L-cells, which are located mainly in the ileum. They are released after food intake and differences have been observed between nor-

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S. Agrawal (ed.), *Obesity, Bariatric and Metabolic Surgery: A Practical Guide*, DOI 10.1007/978-3-319-04343-2_54

mal weight and obese individuals [6]. GLP-1 is an incretin and stimulates the insulin release in response to nutrient ingestion. It exerts its glucose-lowering effects through enhanced insulin secretion in the postprandial state, inhibition of gastric emptying, which blunts postprandial glycemia, and inhibition of glucagon secretion. It also plays a significant role in the regulation of energy homeostasis as it acts on the central nervous system to induce satiety and decrease food intake.

PYY is a peptide released into the circulation with GLP-1 following food ingestion. PYY is released in proportion to the calories ingested and has an inhibitory effect on gastrointestinal mobility. It increases satiety, reduces food intake and delays gastric emptying, but does not affect glucose homeostasis [6].

Similarly, OXM has very little direct influence on glucose levels, but can reduce food intake while increasing energy expenditure [7, 8]. This can result in weight loss. It is cleaved from proglucagon like GLP-1, and can act at the GLP-1 receptor [8]. However, it also has GLP-1 receptor independent activity [8].

Ghrelin is a peptide mainly produced from the X/A-like cells in rodents and P/D1 cells in humans in the fundus of the stomach and acts on the hypothalamus to regulate appetite. It is an orexigenic hormone and stimulates appetite and food intake. Ghrelin also stimulates insulin counter-regulatory hormones, suppresses the insulin-sensitizing hormone adiponectin and inhibits insulin secretion, all of which acutely elevate blood glucose levels. Circulating ghrelin concentrations increase with fasting and decrease following nutrient ingestion in normal weight subjects, but in obese populations the dynamic responses are attenuated [6].

We will review the potential mechanisms involved in weight loss and glucose homeostasis in the four major bariatric procedures: Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), adjustable gastric banding (AGB), and vertical sleeve gastrectomy (VSG).

54.2 Mechanisms of Weight Loss

54.2.1 Malabsorption and Reduction of Stomach Size

As was the case with other bariatric procedures, RYGB was initially designed to combine malabsorption and restriction. However, over the decades since its introduction, it is now established that serum albumin levels remain normal, and levels of fecal fat are minimally altered after RYGB [9, 10]. Patients after RYGB usually complain of constipation and the reduction in combustible energy absorption is low [9]. Therefore, calorie malabsorption is not a major mechanism of weight loss in RYGB and other mechanisms play a greater role (Fig. 54.1). However, malabsorption may become more important in those with shorter lengths of the intestinal limbs or in those who maintain high-fat diets post-RYGB.

RYGB does reduce stomach volume, but food is usually not present within the smaller stomach pouch as it progresses rapidly to the small bowel. In those cases with gastrojejunal stenosis, food in the pouch may result in early gastric distension and subsequently lead to early discomfort and reduced meal size [11]. In the absence of a pylorus, gastric pouch emptying is fast after RYGB. The expectation could reasonably be that reduced stomach volume would result in a compensatory increase in appetite for calorie-dense food to counter weight loss, but this does not appear to be the case.

RYGB recipients report reduced hunger, increased satiety, and a lower consumption of energy dense foods as compared to their preoperative state [12]. Therefore, it is not simply a matter of gastric pouch size; randomized controlled trials have shown that vertical banded gastroplasty (VBG) with reduction in pouch size for example, results in less weight loss and less change in food preferences as compared

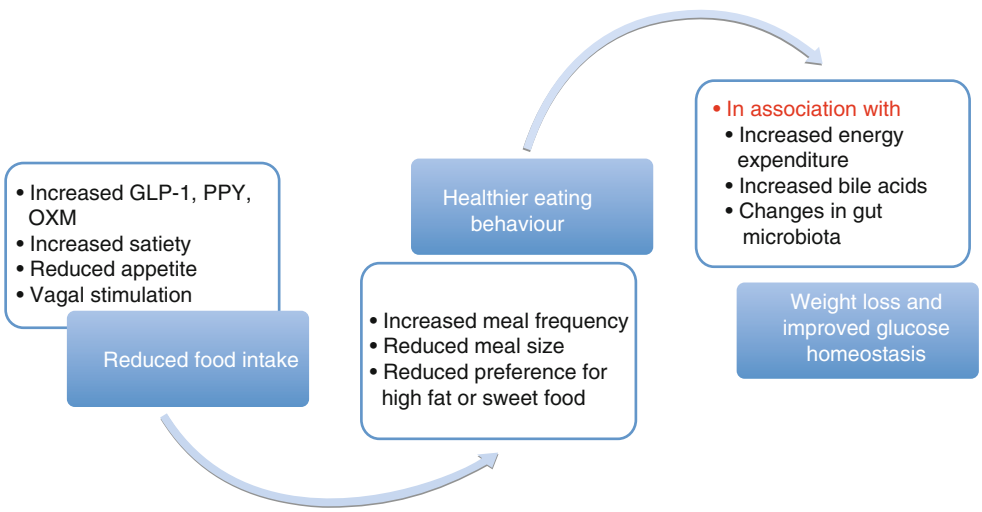

Fig. 54.1 Roux en Y Gastric Bypass (RYGB): The design of RYGB reduces stomach volume but food does not usually rest in the gastric pouch, instead moving rapidly into the small bowel. Modern procedures do not produce significant malabsorption, however, shorter intestinal limbs can limit absorption and result in nutrient deficiency. Key features of this procedure include exclusion of the duodenum and increased delivery of nutrients to the ileum. Transection of vagal fibers during gastrectomy may also be important

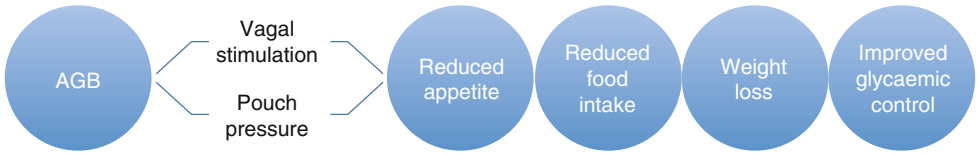

Fig. 54.2 Adjustable Gastric Banding (AGB): This procedure limits the rate of food emptying from the esophagus to the stomach by applying pressure to the stomach inlet. This pressure can be adjusted by inflation or deflation of the band, and may modulate neural signalling producing effects on satiety

to RYGB [13]. This supports the notion that other mechanisms are responsible for the effects of RYGB.

AGB reduces the rate of food emptying from the esophagus to the stomach by regulating the stomach inlet. The pressure on branches of the vagal nerve in the upper gastro-esophageal junction can lead to early satiety (Fig. 54.2) [12]. The lack of compensatory, high calorie seeking behavior in the majority of patients after AGB suggests that the pressure on the upper gastro-intestinal junction alone may not be the only mechanism in weight loss and that other mechanisms may be involved to modulate appetite and food preference. However, this remains to be proven.

Gastric emptying is not altered after AGB, and the rapid weight regain seen after reversal of AGB argues for the physiological attenuation of appetite when the band is optimally adjusted [12]. Much work currently focuses on the role of the vagus nerve in AGB and the associated changes in appetite and satiety. Altered neural signaling is likely to have a role, as gut hormone secretion is not affected by this procedure. This has yet to be conclusively demonstrated in humans [14]. There are no data that demonstrates malabsorption in AGB.

BPD has a malabsorptive effect. BPD recipients can consume over 3000 kcal daily and still maintain weight loss in the long-term [15]. The accompanying high incidence of hypoalbuminemia after BPD confirms the risk of malabsorption [15].

Stomach size is reduced after BPD, but not to the same extent as RYGB. Gastric emptying can be marginally accelerated compared to the non-operated state but is not nearly as fast as after RYGB. Gut hormones such as PYY and GLP-1 are also increased in the post-prandial state [16]. This may reduce the hyperphagia caused by the calorie malabsorption. Multiple mechanisms are likely to be important in mediating the effects of BPD (Fig. 54.3).

In VSG, a non-significant increase in fecal caloric density has been demonstrated in animal models [17]. However, this has not been replicated in humans. Consequently, the contribution of caloric malabsorption to the weight loss after VSG is currently considered to be minimal (Fig. 54.4). There is significant controversy as to whether the gastric sleeve volume in VSG correlates with food intake and body weight reductions. Some studies have shown that larger gastric pouches or stomas result in less weight loss [18, 19]. Others do not find any relationship between these variables [20–22].

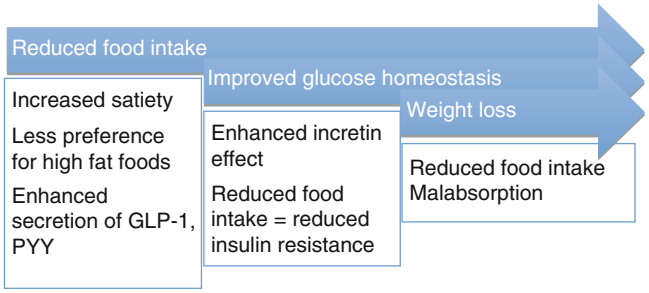

Fig. 54.3 Biliopancreatic Diversion (BPD): BPD is a complex procedure involving many physiological mechanisms, but is the only modern major form of bariatric surgery that could be considered a malabsorptive procedure due to the extensive intestinal bypass central to its design

Similarly, the data on the effect of gastric sleeve volume on weight loss after VSG are inconsistent [23–26]. These inconsistencies may be due to the variation in the measurement of gastric volume. Nonetheless, the lack of a clear association between gastric volume and weight loss to date suggests that the physiological consequence and not the anatomical size of the reduced stomach is important.

Counter to the initial hypotheses of the VSG causing restriction to gastric emptying, intestinal transit appears to be faster postoperatively [27–30]. This may not be the case in surgery where the antrum is preserved [31]. The mechanisms underlying this are unclear but may include the generation of very high intraluminal gastric remnant pressures, the excision of the gastric pacemaker at surgery, and neural signaling (Fig. 54.4). The rapid gastric emptying and intestinal motility may explain why the release of anorexigenic gut hormones after VSG is very similar in magnitude to RYGB.

54.2.2 Changes in Hunger and Satiety

Increased satiety and decreased hunger occur within days following RYGB [32–34]. The changes in the postprandial levels of gastrointestinal hormones that induce satiety, such as GLP-1, OXM and PYY have been proposed as one of the possible contributors to the reduced food intake after RYGB. Increased postprandial PYY, OXM, and GLP-1 responses are observed from the second postoperative day after RYGB, prior to any significant weight loss, and correlate with differ-

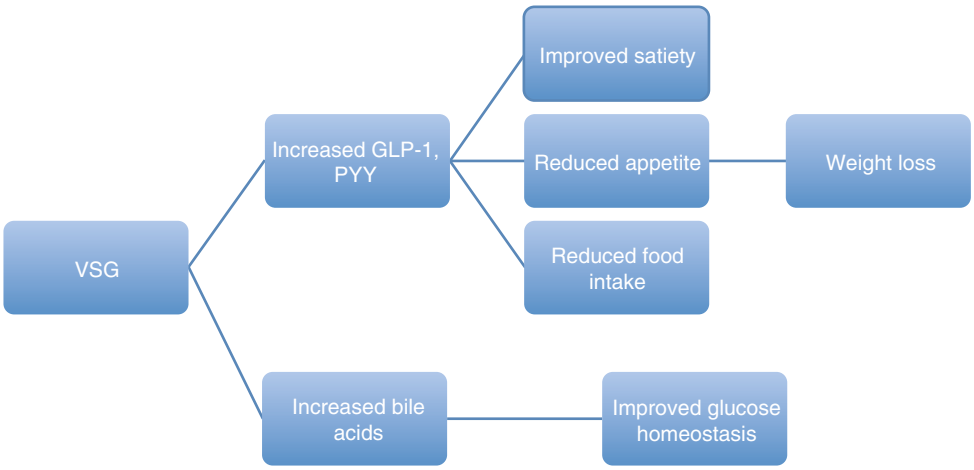

Fig. 54.4 Vertical Sleeve Gastrectomy (VSG): This procedure reduces stomach volume, but does not alter nutrient flow. The contribution of caloric malabsorption is considered to be minimal. It may be that physiological changes, such as gut hormone secretion for example, are more important than the reduction in stomach volume. VSG does not appear to cause restriction, but instead increases intestinal transit time, potentially due to the generation of high intraluminal gastric remnant pressures, the excision of the gastric pacemaker at surgery, and neural signalling

ent levels of weight loss [17]. Moreover, inhibition of the gut hormone responses with a somatostatin analogue (octreotide) in patients after RYGB results in an increase in food intake, suggesting that gut hormones are important in mediating the reduced calorie consumption seen after RYGB [33].

Changes in appetite are also reported following AGB [32–34]. The changes in the postprandial levels of gastrointestinal hormones that induce satiety, such as GLP-1 and PYY, are not seen in AGB, and inhibition of the gut hormone responses with octreotide does not affect food intake in AGB recipients [33, 34]. The vagal nerve plays an important role in the regulation of food intake and body weight, and it is likely that AGB exerts its effects on satiety by neural signaling arising from the upper gastro-esophageal junction [12]. This is suggested by data that show increased satiety associated with increased pouch pressure [35]. Pouch emptying rates and changes in pouch pressure are not associated with satiety. Therefore, the dilatation or pressure effect on the gastric pouch produces a satiation effect in the absence of any consistent change in gut hormones [34].

The vagal nerve also plays an important role in the regulation of food intake after RYGB [36]. Vagal afferents are activated by the presence of nutrients in the stomach and the intestine, and the preservation of vagal fibers during surgery leads to greater and more sustained body weight loss in animal models of RYGB [36]. Similarly, pressure generated in the proximal alimentary limb of the RYGB by a 20 mL balloon appears to predict the meal size of a patient. Thus, the rapid entry of food from the esophagus, through the small gastric pouch and the larger gastro-jejunostomy, may trigger neural signals in the alimentary limb, which may contribute to the long-term weight maintenance after RYGB [22, 37].

Satiation is increased in BPD recipients for up to 2 years postoperatively [38]. There is also a change in food preference with an increased aversion to sweet tastes [39]. While there are very little data on these mechanisms after BPD, similar changes to the gut hormone profiles and mediation of vagal activity are likely to be involved as in RYGB (Figs. 54.1 and 54.3).

54.2.3 Changes in Energy Expenditure

Chronic caloric deprivation as observed after RYGB normally produces a decrease in resting energy expenditure [40]. However, resting energy expenditure has been shown to increase after RYGB in rodents, and this may contribute to the postoperative weight loss [40, 41]. The data on energy expenditure in humans are controversial and inconsistent. In patients with a normal preoperative metabolic rate, resting energy expenditure decreases over time, whereas patients who have low metabolic rates before RYGB can exhibit increases in their resting energy expenditure postoperatively [40]. These changes occur after RYGB despite the very low-calorie diet. Other studies have found lower resting energy expenditure after RYGB [42]. These discrepant results may be a result of the difficulty in measuring energy expenditure in humans, and a reliance on indirect calorimetry as the primary measurement method.

Energy expenditure over 24 h appears to be increased up to 9 years postoperatively [43]. Much of this effect is due to increases in postprandial energy expenditure, which is associated with postprandial increases in GLP-1 and PYY. GLP-1 would be expected to reduce energy expenditure, but may affect an increased rate of energy use in conjunction with glucagon in humans [44]. Therefore, changes in energy expenditure after bariatric surgery may not be attributable to one single hormonal change, but to a combination of changes. The increase in small bowel mass and metabolism after RYGB in rodents, and potentially humans, may explain the changes in postprandial energy change, and to some extent, the basal metabolic rate.

Measurements of energy expenditure in VSG or AGB rat models, in which the only anatomical alteration is the

reduction of stomach size, do not reveal significant changes in energy expenditure [45, 46]. Resting energy expenditure after VSG has only been assessed in rodent models which have demonstrated either stability [45] or a trend for a decrease [17]. In studies of AGB, a decrease in energy expenditure at rest has been demonstrated [47, 48]. However, the data is not consistent and other results report an increase in expenditure when corrected for body weight [49]. These discrepancies likely arise from the variability in the methodologies used to quantify body composition, and the inherent limitations of indirect calorimetry and the assessment of subjects with different food intake at different time points after surgery.

Resting energy expenditure in humans decreases significantly after BPD to the level of normal weight controls [50]. However, energy expenditure related to physical activity increases after BPD compared to the preoperative level [50, 51]. There are also increases in diet-induced thermogenesis and carbohydrate oxidation after BPD [51]. The increased energy expenditure is likely to contribute towards sustained weight loss in BPD recipients. As with other procedures, the mechanisms to explain this are not defined, but the increase in small bowel mass, which is more pronounced after BPD than RYGB, may play a role.

54.2.4 Changes in Food Preferences

The orbitofrontal cortex, hypothalamus, brainstem and corticolimbic areas in the brain co-ordinate the processing of sensory information and energy homeostasis, and regulate food searching, sensing and reward. Higher cortical centers are implicated in psychological and emotional factors, which can influence food intake beyond homeostatic requirements [52]. Neuroimaging studies show that this reward network is dysfunctional in obese cohorts [53].

RYGB recipients tend to have reduced meal size but increased meal frequency postoperatively [54]. In randomized controlled experiments, VBG recipients consumed a higher proportion of fat and carbohydrates compared to RYGB recipients, who preferred fruit and vegetables instead of high-fat food [13]. RYGB recipients consume less solid and liquid sweets and less dairy products compared to VBG recipients, consequently producing an avoidance of calorie dense foods, and a preference for high glycemic index foods [29, 55]. The reward areas of the brain are activated in response to high calorie food to a lesser extent after RYGB [56, 57]. Animal models of RYGB report an avoidance of sweet and high-fat foods compared to sham animals [58–60].

The data on food preferences after AGB suggest that there may be a reduction in appetite for palatable foods (hedonic drive) after AGB [61]. However, specific data on preferences for fats or carbohydrates are not available. In VSG, there are no human data, and the rodent data are conflicting. In these results, rats exhibit either no change in food constituent preference or changes which are comparable to RYGB [17, 60, 62]. Further work is needed in non-RYGB bariatric surgery to define the effect on food preferences in these procedures.

54.3 Mechanisms of Improved Glucose Homeostasis After Bariatric Surgery

54.3.1 The "Hindgut and Foregut" Theories

Maintained weight loss clearly plays an important role in the improved glucose homeostasis after RYGB. This is evident in the restoration of glucose tolerance and improvement of insulin sensitivity by all types of bariatric surgery. The enforced caloric restriction reduces hepatic insulin resistance after all bariatric procedures. The ability of acute caloric restriction to transiently improve glycemia in T2DM is well established, and by the time patients return to an unrestricted diet, they begin to experience the peripheral insulin-sensitizing effects of weight loss [63]. However, if caloric restriction played the only role in mediating changes in glucose homeostasis, then improvements in glucose homeostasis would be equivalent after all types of bariatric surgery. RYGB produces greater effects in glucose homeostasis than AGB and VSG, and these effects are independent of weight loss [64, 65].

The "hindgut" hypothesis postulates that the improved insulin secretion after RYGB is due to increased rapid delivery of nutrients to the distal gut, which causes enhanced secretion of gut hormones such as GLP-1 and PYY. This theory could partially explain the significant effectiveness of VSG and RYGB on glucose homeostasis from the early postoperative period. Support for this hypothesis comes from experiments involving ileal interposition [63, 66]. In this operation, a segment of the L-cell-rich ileum is transplanted into the upper intestine, near the duodenum-jejunum boundary, thereby increasing its exposure to ingested nutrients [66]. This operation significantly increases the postprandial GLP-1 response and results in improved glycemic control without any malabsorption or gastric restriction [66].

According to the "foregut hypothesis," bypass of the proximal small bowel reduces the secretion of unknown gastrointestinal factors that decrease insulin secretion and promote insulin resistance. Therefore, duodenal exclusion could reduce production of these putative 'anti-incretins' leading to an increase of insulin secretion [67]. Duodenal exclusion and correction of the anti-incretin dysfunction, may explain the improvement of T2DM after RYGB. Additional evidence supporting the foregut hypothesis comes from studies examining the effects of preventing nutrient contact in the proximal gut by inserting a duodenal jejunal bypass liner into the duodenum

which extends into the jejunum and results in early improvement in glucose homeostasis after insertion [68].

54.3.2 Bile Acids

Alterations in the levels or types of bile acids in the gut or the circulation after bariatric surgery have been implicated in the improvements in glucose homeostasis observed after RYGB. Bile acids levels, both total and sub-fractions, in the plasma are increased after RYGB [47, 69–71]. Plasma bile acids are also elevated in animal models of VSG [72]. This is in contrast to AGB, where plasma bile acid levels are unaffected. The level of bile acid fractions in plasma negatively correlates with glycemic excursions, implicating bile acids as agents in glucose homeostasis [69].

Bile acids can directly or indirectly affect glycemic control through the TGR5 receptors or nuclear FXR receptors and the release of fibroblast growth factors. There may be a central effect on food intake and appetite, as bile acids can cross the blood–brain barrier and act on receptors in the hypothalamus [73–77]. This could conceivably contribute towards improved glycemic control. In the absence of detailed mechanistic studies, the exact role of bile acids as mediators of weight loss and glycemic control after RYGB is unclear.

54.3.3 Gut Microbiota

Gut microbiota in the context of obesity and weight loss have also been identified as important metabolic mediators after bariatric surgery. Bacteria that are more efficient in extracting energy from nutrients and storing it as fat have been implicated as contributing towards the development of obesity [78]. A depletion of Prevotellaceae, Archea, Firmicutes, Bacteroidetes colonies, and an increase in the Bacteroidetes/Prevotella ratio and Gammaproteobacteria of this flora has been observed after RYGB [79–81]. These alterations may be due to changes in dietary macronutrient composition, anatomical manipulations and pH, but altered bile flow may also be a major determinant of change in gut microbiota.

The microbiota may change as a result of surgery, but they also affect the surgical recipient. The transfer of the gut bacteria from RYGB to un-operated germ free mice leads to weight loss, and this may be the result of increased energy expenditure [82]. However, the exact mechanisms through which gut bacteria contribute to weight loss remain to be determined.

Conclusion

There are multiple mechanisms that contribute to weight loss and improvements in glucose homeostasis after bariatric surgery (Figs. 54.1, 54.2, 54.3, and 54.4). Many of these are due to the anatomical rearrangements of the gut, which produce powerful physiological changes and which may alter gut microbiota. Each procedure utilizes these mechanisms to different extents, and therefore can produce different clinical outcomes and side-effect profiles. A full understanding of these mechanisms may lead to the optimization and personalization of these procedures but also the development of more effective and safe pharmacotherapy for the treatment of obesity and T2DM.

Key Learning Points

- Bariatric surgery is the most effective treatment for long-term weight loss and to optimize glycemic control in type 2 diabetes mellitus.
- Each major procedure acts through various mechanisms including reduction in hunger, increase in satiation, changes in food preferences, increasing energy expenditure, altering bile acid, gut hormone and vagal signaling.
- The contribution of each of these mechanisms varies with procedure.
- Understanding the mechanisms of action of these procedures may accelerate their optimization and the development of medical and surgical therapies for obesity and type 2 diabetes mellitus.

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