Physiological Mechanisms of Bariatric Procedures

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Chapter Objectives

1. Describe some of the most commonly accepted theories regarding the physiological mechanism of bariatric procedures.
2. Address the potential physiological mechanisms affecting both weight loss and resolution of diabetes.

Introduction

In spite of the fact that obesity has reached pandemic proportions, it remains one of the most neglected public health problems in the United States. This has awakened a growing interest in placing obesity as a prime subject of many recent public health campaigns. The need for these considerable efforts derives from the alarming reports of the prevalence of obesity in the US population. In 2015–2016, the prevalence of obesity was 39.8% in adults and 18.5% in adolescents [1].

Despite the increased awareness of its severity, the linear time trend forecasts suggest that by 2030, 51% of the US population will be obese [2]. The progressive and continuous rise in the prevalence of obesity have also determined a secondary epidemic of the related comorbidities, in particular the risks of cancer, diabetes, and cardiovascular diseases.

Bariatric surgery is now considered the first management option for failure of medical treatment in severely obese subjects and the most effective method for sustained long-term weight loss. There is extensive evidence of the positive metabolic impact, remission, and resolution of most of the comorbidities associated with severe obesity, diabetes included [3]. Historically, bariatric procedures are thought to induce weight loss by causing caloric restriction and/or malabsorption. However, newer mechanistic studies, in parallel with the establishment of the gastrointestinal tract as a key regulator of energy and glucose homeostasis, have introduced the hypothesis that alternative mechanisms mediate the weight-reducing and metabolic benefits of most bariatric/metabolic operations. Furthermore, as the close interaction between diet, gut, and brain hormones unwinds, the mechanisms of action of these procedures, as well as their classification, have significantly changed. In fact, the pathway describing how the centrally regulated body weight homeostasis is profoundly influenced by hormones secreted in the intestinal tract and adipose tissue is now well recognized [4]. The overall balance of these peripherally secreted hormones and their interaction at the level of the hypothalamus would eventually affect food intake and energy expenditure [5].

The mechanism of diabetes resolution after bariatric surgery is not entirely understood. Since insulin resistance is one of the main etiologies, it seems obvious that weight loss, although not the only component, continues to be an essential contributor. In fact, typically diabetes improvement or resolution occurs within weeks after bariatric procedures. Regardless if it is gastric bypass (GBP), sleeve gastrectomy (SG), or biliopancreatic diversion (BPD), in all of these procedures, remission ensues from the preceding and expected weight loss [6, 7]. Pories et al. were the first to suggest that caloric restriction played a key role in the resolution of diabetes; following this historical finding, the important glucoregulatory roles of the gastrointestinal (GI) tract were 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., currently other hypotheses involving changes in bile acid metabolism; GI tract nutrient sensing and glucose utilization, incretins, and possible anti-incretin(s); and the intestinal microbiome have gained strength. According to recent studies, these changes, acting through peripheral and/or central pathways,

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lead to reduced hepatic glucose production, increased tissue glucose uptake, improved insulin sensitivity, and enhanced ß(beta)-cell function. These findings suggest that a constellation of factors, rather than a single domineering mechanism, likely mediates postoperative glycemic improvement, with the contributing factors varying according to the surgical procedure [8]. Nevertheless, all coincide in one common positive effect resulting in the resolution of diabetes.

Here, we describe some of the most commonly accepted theories regarding the mechanism of action of the most widely accepted bariatric procedures.

Mechanism of Action

The current understanding of different mechanisms of action of these procedures, in particular the role of gut hormones, has led to dispute the traditional classification of bariatric procedures in the three main categories: restrictive, malabsorptive, and combined. Although a clear understanding of all the mechanisms of action of bariatric procedures has not been reached, multiple theories exist. It is likely that several factors contribute to the final efficacy of the procedures. Because of the overlap of effects, we will address the potential mechanisms of action affecting both weight loss and diabetes resolution. Potential contributors to weight loss and diabetes resolution are outlined in Table 5.1.

Malabsorption

As previously mentioned, the surgically induced alterations of the normal gastrointestinal absorption process lead to various degrees of weight loss. This is especially true in procedures such as the BPD and the BPD with duodenal switch (BPD-DS) where long alimentary (250–300 cm) and biliopancreatic limbs leave a short (100 cm) common channel for the absorption of nutrients. Even the more conservative alimentary limb lengths (100–150 cm) of the standard gastric bypass have been shown to create a certain degree of fat malabsorption, as demonstrated by the increase in fecal fat at 6 months (126%) and 12 months (87%) [9]. Since there is no significant alteration of the protein and carbohydrate absorption, the overall reduction of the combustible energy absorption has been shown to be only 6–11% [10]. While it is true that the more malabsorptive procedures (BPD, BPD-DS) result in a more impressive weight loss (excess weight loss [EWL], 79%) and diabetes resolution (98.9%), it is unlikely that the malabsorption by itself is solely responsible [11].

Table 5.1 Potential mechanisms of action of bariatric operations

	Procedure				
Mechanism of action	RYGB	LSG	LAGB	BPD	BPD-DS
Malabsorption	±	–	–	+	+
Caloric restriction	+	+	±	+	+
Energy expenditure	±	–	–	+	+
Δ(Delta)-eating behavior	+	±	–	?	?
Hormonal	+	+	–	+	+
Vagus nerve	?/–	?/–	?/–	?/–	?/–
Bile salts	+	+	±	+	+
Adipose tissue	+	+[a]	–	+	+
Microbiota	±	?	–	±	±
ß(Beta)-cell function	±	?	–	±	±
Insulin sensitivity	±	+	+[a]	++	++

[a]Only related to weight loss

Caloric Restriction

Caloric restriction is one of the immediate effects of RYGB and SG due to anatomical changes. The beneficial effect of caloric restriction on the glycemic control has been previously demonstrated [12]. The carbohydrate-controlled calorie-restricted diet produces up to 40% improvement of the insulin resistance and ß(beta)-cell function as measured by the homeostatic model assessment (HOMA) method in just 2 days [13]. If continued over a period of 11 weeks, the diet can improve the peripheral insulin resistance, even if the hepatic insulin sensitivity remains unchanged [13]. In the perioperative period of bariatric surgeries, the caloric intake is dramatically reduced to 200–300 kcal/day. This factor undoubtedly contributes to the immediate weight loss experienced by these patients postoperatively. In fact, some authors were able to demonstrate similar weight loss results in non-operated obese subject after 4 days of post-Roux-en-Y gastric bypass (RYGB) diets [14]. The rate of secretion of gastrointestinal hormones, however, was altered in the RYGB group [14]. These findings were replicated by other authors who found similar results in weight loss at short-term follow-up comparing RYGB and low-calorie diet, but only RYGB patients determined improvements of insulin resistance, insulin secretion, and insulin-stimulating gut hormones, such as GLP-1 [15]. This is obviously true only for the first few weeks. In fact, there is a significant difference in the rate of weight loss, as demonstrated by the time needed to lose 10 kg between RYGB (30 days) and caloric restriction (55 days) [16]. Also, if the caloric restriction was the only responsible mechanism for glucose control, the improvement of this parameter should be uniform between the different bariatric operations. It has been clearly demonstrated how BPD ± DS, RYGB, and laparoscopic sleeve gastrectomy (LSG) provide a quicker improvement of diabetes as compared to laparoscopic adjustable gastric banding (LAGB) [11, 17]. This is also demonstrated by the change in the profiles of the glucose and insulin curves between LAGB, low-calorie diets, and RYGB. In fact, if LAGB and a low-

calorie diet produce a downward shift of such curves, RYGB determines shortened times to peak glucose and insulin with a leftward shift of the curves [18].

It is reasonable to conclude that, although caloric restriction is an important factor contributing to the improvement in hepatic insulin sensitivity, it likely plays a role only in the immediate postoperative period, and other factors are involved in the long-term weight loss and glycemic control improvement.

Energy Expenditure

Under normal circumstances, the energy expenditure decreases consequently to caloric restriction and the resulting weight loss [19]. This adaptive mechanism on one hand is meant to preserve the individual and on the other hand could be responsible in part for the long-term failure of the caloric restrictive diets. The data on energy expenditure after bariatric surgery is somewhat conflicting. In fact, if some investigators found a decrease in energy expenditure secondary to the weight loss after RYGB, others were able to demonstrate its increase in both RYGB and BPD, but not after vertical banded gastroplasty (VBG) [15, 20–22]. There is data that shows evidence of significant reduction of resting energy expenditure and a significant degree of metabolic adaptation both occur after sleeve gastrectomy. The hypothesis is that a greater metabolic adaptation could be partly responsible for a lower weight loss after surgery. Furthermore, there is recent evidence that suppression in resting energy expenditure after sleeve gastrectomy and RYGB remained up to 2 years, even after weight loss had plateaued. This study suggests that energy adaptation is not a contributing mechanism to medium-term weight maintenance after SG and RYGB bariatric surgeries. No definite conclusions on the role of energy expenditure can be drawn at this time, and additional mechanisms should be sought to explain the metabolic improvements after bariatric surgery.

Changes in Eating Behavior

The consumption of diets high in fat has been associated with the development and maintenance of obesity in both humans and rodents [23, 24]. Also obese individuals have a greater propensity to choose high-fat foods, as compared to lean ones [25]. On the other hand, it is known how the eating behaviors change after bariatric surgery.

In fact several studies have shown the predilection of lower-fat foods after RYGB [26, 27]. More recently, food choices after SG have been studied in rats [28]. Similarly to what is found after RYGB, in spite of the different anatomic alterations, post-SG rats preferentially choose low-fat and avoid calorie-dense diets [28]. These findings cannot only be explained by the mechanical restriction, as a compensatory choice of more calorie-dense foods to maximize caloric intake would have occurred.

Other options to explain such behaviors include postoperative changes of the taste acuity and neural responses to food cues. Two studies have shown enhanced taste acuity and altered hedonic craves for food in post-RYGB patients [29–31]. This has been validated by functional magnetic resonance imaging (fMRI) studies of RYGB patients who presented reduced activation of the mesolimbic reward areas, especially after high-calorie foods [32].

Other possible mechanisms include the aversive symptoms proper of some of the bariatric operations derived by improper food choices. In particular, the development of the uncomfortable symptoms of the dumping syndrome might steer patients away from high caloric carbohydrates. Unfortunately, no scientific evidence on the impact of aversive symptoms and weight loss exists. Occasionally, the aversion to certain foods promotes the development of maladaptive eating behaviors, which ultimately affect the weight loss process. The underlying behavioral and physiological mechanisms of the described phenomenon seem to be complex. However, results from animal models of bariatric surgery indicate that learning processes may play a role as changes in diet selection progress with time in rats after RYGB.

Entero-Hormones, Incretins, and Intestinal Adaptation

Gut hormones play a crucial role in regulating appetite, satiety, food intake, systemic metabolism, and insulin secretion. Different degrees of evidence support the physiological roles for ghrelin, CCK, GLP-1, and PYY in GI motility [8]. An important feature of these relationships is that gastric volume, gastric emptying, intestinal-nutrient sensing, and the secretion of these four hormones are linked in negative-feedback loops. Changes in GI hormone secretion provide plausible mechanisms for the remarkable therapeutic efficacy of bariatric surgery. Interestingly, similar changes have been seen between patients who have undergone SG and those who have undergone RYGB [8]. 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. Analysis using 2-deoxy-2-[18F] fluoro-D-glucose in rodents and humans show that the alimentary limb becomes a major site for glucose disposal.

These changes are likely to contribute to improved glycemic control. In contrast, there is no evidence of GI tract hyperplasia after SG. However, the number and density of cells containing GLP-1 reportedly increase after SG in rodents. Moreover, SG reduces intestinal glucose absorption, potentially contributing to improved glucose tolerance [8]. These findings yet again highlight that RYGB and SG improve glucose homeostasis by different as well as overlapping mechanisms.

Entero-Hormones

The ingestion of food determines alterations of the gastrointestinal, endocrine, and pancreatic secretions, known as the enteroinsular axis. The main modulators of such mechanism, including GLP-1, GIP, peptide YY, oxyntomodulin, cholecystokinin, and ghrelin, have been found altered after some bariatric surgery procedures (RYGB, BPD-DS, VSG) (Table 5.2).

Glucagon-Like Peptide-1 (GLP-1)

This is a peptide released by the L cells of the ileum and colon in response to the ingestion of meals. Overall, it is an insulinotropic hormone, and as such, it is responsible for the increase of insulin secretion in response to oral glucose (*incretin effect*). Additionally it has been linked to stimulate ß(beta)-cell growth, decreasing their apoptosis and, ultimately, increasing their mass in rats [33]. The modulating effect of GLP-1 on postprandial glycemia is also achieved by suppression of glucagon secretion, decreased gastric emptying, and intestinal motility (*ileal brake*), as well as central nervous system pathways to induce satiety [33, 34]. Overall GLP-1 enhances satiety and reduces food intake. Normally GLP-1 secretion is stimulated by the presence of nutrients in the distal ileum. This is one of the theories to explain the rapid (within days post-procedure) and durable hormonal increase demonstrated after the metabolic procedures with intestinal bypass (RYGB, BPD, BPD-DS) [35–37]. Bypass of a proximal gut ("foregut") and the increased distal gut ("hindgut") L-cell nutrient exposure are two potential explanations for the altered gut hormone profile observed after RYGBP. However, the burden of evidence is in favor of the latter. Enhanced GLP-1 responses are also observed after SG, despite the absence of alteration in the route of nutrient delivery.

In RYGBP, nutrients rapidly pass through the small gastric pouch, bypassing the majority of the stomach and upper small bowel and directly entering the mid-jejunum. In SG, the removal of the gastric fundus and body results in an unaltered route of nutrient passage through the GI tract [38, 39]. Both procedures result in accelerated gastric emptying and a rapid entry of undigested food into the jejunum. Consequently, there is enhanced direct contact of nutrients with the apical surface of L cells, interspersed among intestinal epithelial cells, resulting in Ca2-dependent stimulation of GLP-1 secretion into intestinal small blood vessels [40, 41].

Additional mechanisms to explain the GLP-1 increase are related to the inhibition of the GLP-1 degrading enzyme dipeptidyl peptidase-IV (DDP-IV) demonstrated after RYGB and not in type II DM [42]. Once again the evidence is discordant as increased levels of DDP-IV have been reported after BPD [43].

Finally, the role of the GLP-1-induced hunger modulation and decrease in food intake on the weight loss after bariatric operations remain controversial. Evidence for a link between GLP-1 response and weight loss is at best correlative, and a causal relationship has not yet been established. In fact, although the procedures that present the more pronounced weight loss are also the ones determining the highest levels of GLP-1, the increased satiety does not correlate with a significant increase of GLP-1 on longer follow-up studies [44, 45].

We can conclude that although GLP-1 is not the main direct responsible for the weight loss after bariatric operations, it contributes to some weight loss, and it is likely a key contributor to the glycemic homeostasis proper to these procedures.

Glucose-Dependent Insulinotropic Polypeptide (GIP)

The K cells of the duodenum and proximal jejunum mainly secrete this hormone. Its secretion is enhanced by the presence of nutrients (especially carbohydrates and lipids) in this portion of the intestine. As the name indicates, this is an insulinotropic hormone, although less powerful than GLP-1, determining increased postprandial insulin secretion and pancreatic ß(beta)-cell augmentation [46]. Contrary to GLP-1, GIP has no effect on the intestinal and gastric motility. GIP also affects lipid metabolism by increasing lipogenesis and promoting fat deposition [33]. The function of GIP in diabetic patients is less clear, although consistently demonstrated to be impaired [47]. Due to its site of secretion, GIP has been regarded as one of the hormones possibly involved in the foregut theory. The changes seen in this hormone in animal models of bariatric surgery have not been consistent. Most human studies have reported a decrease in this hormone post-malabsorptive surgery. The effects of bariatric surgery on GIP are discordant, although in general more evidence exists on the decreased levels of this hormone after RYGB and BPD, likely from bypassing the proximal intestine, than the contrary [38, 48]. In contrast, no changes in

Table 5.2 Characteristics of entero-hormones after bariatric operations

	Origin	Satiety	Glycemic control	GI motility	RYGB	LSG	LAGB	BPD	BPD-DS
GLP-1	L cells	↑	↑	↓	↑	↑	No Δ(delta)	↑	↑
GIP	K cells	No Δ(delta)	↑	No Δ(delta)	↓	Unknown	No Δ(delta)	↓	↓
PYY	L cells	↑	↑ or no Δ(delta)	↓	↑	↑ or no Δ(delta)	No Δ(delta)	↑	↑
Oxyntomodulin	L cells	↑	↑	↓	↑	↑	No Δ(delta)	↑	↑
CCK	I cells	↑	No Δ	↑	?	↑ or no Δ(delta)	Unknown	Unknown	Unknown
Ghrelin	Oxyntic	↓	No Δ	No Δ	↓	↓↓	No Δ(delta)	No Δ(delta)	↓↓

GIP levels are reported after LAGB [38]. The changes of GIP after LSG remain undetermined. Overall the role of GIP in the mechanism of action of bariatric procedures remains elusive.

Peptide Tyrosine Tyrosine (PYY)

PYY is also expressed in the endocrine pancreas, where PYY may have paracrine intraislet actions. Also, PYY is expressed by neurons in the gigantocellular reticular nucleus of the rostral medulla, which have widespread central projections. PYY activates several neuropeptide Y-family receptors (NPYR), including NPY1R (or Y1R), NPY2R, NPY4R, and NPY5R, whereas PYY is selective for NPY2R. NPY2R are expressed throughout the body, including in several brain regions, the GI tract, and vagal afferents [49–51].

PYY may contribute to gastric emptying via the ileal brake mechanism, to the inhibition of eating, and to the control of meal-related glycemia, but the evidence that these are physiological actions remains scarce. Similarly, PYY role in RYGB remains unclear. This modest progress may be due in part to the difficulties of PYY research, including the low threshold for eliciting illness with PYY infusions, the lack of NPY2R antagonists for human use, and the possibility of neuropod PYY signaling. After RYGB, plasma levels of PYY increase modestly (20%) in the fasting state and by 3.5-fold in the postprandial state [51].

Similarly, postprandial levels of PYY increase 1 year following VSG. 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, and infusion of anti-PYY antibodies increases food intake in postbypass rats. Thus, enhanced PYY secretion may contribute to weight loss after RYGB [52–55].

The key role of PYY in the post-bariatric surgery weight loss is supported by encouraging evidence in animal models but needs further dislucidation in human studies which present a challenge given to the current limitations previously discussed.

Oxyntomodulin

Since its polypeptide structure is similar to GLP-1, oxyntomodulin's metabolic pathways present several resemblances both in its food-related secretion and degradation process via the enzyme dipeptidyl peptidase-IV (DDP-IV) [56–58]. Similarly to GLP-1, oxyntomodulin reduces gastrointestinal motility and participates in the regulatory mechanism of glucose homeostasis. As seen for the other two hormones secreted by the L cells—GLP-1 and PYY—oxyntomodulin levels increase after RYGB, but not after LAGB [59]. Because of the overlap in secretion and function, it is difficult to attribute the true value of each one of them in postsurgical weight loss.

Cholecystokinin (CCK)

CCK is normally secreted from the duodenum and proximal jejunum in response to nutrients. CCK has been clearly established as a satiation signal in humans and may contribute to the control of meal-related glycemia both indirectly, via its effect on gastric emptying, and directly via control of hepatic glucose production. Pathophysiology of CCK signaling may contribute to overeating, to obesity and T2DM in some patients, and to early satiation after RYGB. Additionally, CCK plays a key role in gallbladder and gastric emptying and exocrine pancreatic secretion. Preclinical studies indicate that CCK is a candidate for obesity pharmacotherapy, especially in combination with other endocrine-based therapies. However, evidence is still unclear on the changes of this hormone after bariatric surgery. Some have shown an increase after LSG, but its overall role in the mechanism of action of these procedures remains undefined [58].

Ghrelin

Ghrelin (growth hormone-releasing peptide) is a hormone secreted mainly by the oxyntic glands of the fundus of the stomach and in smaller amounts in the rest of the small bowel. As its name implies, it is involved in the secretion of the growth hormone. This is primarily an orexigenic hormone stimulating directly the hypothalamus. Obese individuals present a decreased suppression of ghrelin after a meal [56, 59, 60]. In addition, ghrelin inhibits insulin secretion by an unknown pathway [61]. It seems that, thanks to this latter property, ghrelin suppresses the insulin-sensitizing hormone adiponectin, negatively affecting the glucose metabolism [62]. Because of these negative effects on the glucose homeostasis, the reduction of ghrelin seen after certain bariatric operations could be beneficial for overall glycemic control [62]. Although most of the biological effects of ghrelin are due to its acylated form, the non-acylated equivalent seems biologically active as well [33]. The challenge in identifying the two forms with different assays might explain some of the discordant findings of ghrelin variation after bariatric operations. In general, although it would be reasonable to speculate that bariatric procedures that do not alter the contact of food with the fundic glands (LAGB, BPD) do not determine significant alteration of ghrelin levels, evidence of the opposite exists [63, 64]. However, if some reports have shown the reduction of ghrelin levels after RYGB, others

found no changes or even increases of such levels [57, 65, 66]. In randomized trials, ghrelin levels have been found to be permanently lower after LSG than RYGB, likely due to the complete removal of gastric fundus [67]. Also vagal stimulation might affect ghrelin secretion, and vagotomy has been associated with decreased levels [68], although the role of the vagus nerve on the secretion of ghrelin has been disputed by others [69]. Overall, contradicting evidence exists on the role of ghrelin on the weight loss after bariatric surgery, and this hormone likely plays only a marginal role.

Mechanisms of Diabetes Resolution

The existence of an entero-hormonal mechanism to explain diabetes resolution has been postulated for several years [7]. This is also indirectly proven by the pattern of diabetes resolution after gastric banding that follows the weight loss curve and by the multiple hormonal changes described after gastric bypass [70, 71]. In particular, insulin and leptin levels decrease, whereas GLP-1, GIP, PYY, and ACTH increase even before any significant weight loss [71, 72]. Currently, two main theories exist on the mechanism of diabetes resolution after bariatric surgery: the "foregut" and "hindgut."

Foregut Hypothesis

According to this theory, the exclusion of the duodenum from the pathway of the nutrients will prevent the secretion of an unidentified "anti-incretin" substance. In fact, diabetes mellitus (DM) could be due to the overproduction of an "anti-incretin" that determines decreased insulin secretion, insulin resistance, and depletion of the β(beta)-cell mass. When the food bypasses the duodenum, this "anti-incretin" is inhibited. Among the advocates for this theory, Rubino et al. have elegantly demonstrated the resolution of diabetes in rats in which the duodenum was surgically bypassed and excluded [73]. The restoration of duodenal passage in the same group of animals resulted in recurrence of the impaired glucose tolerance state. Others believe that the glucose absorption changes after duodenal bypass. In fact, it has been previously described in a rodent model that both the intestinal morphology and the Na^+/glucose cotransporter 1 (SGLT1) function are altered after gastric bypass [74]. In particular, the villous height and crypt depth of the intestinal segments exposed to nutrients are increased, but, unexpectedly, the glucose transport activity is decreased. According to the authors, this could be one of the mechanisms involved in the improvement or resolution of diabetes after duodenal exclusion procedures, such as gastric bypass. Although the process by which duodenal exclusion leads to decreased glucose transport is unclear, some authors have speculated that the interruption of the proximal intestinal regulation of SGLT1 via the sweet taste receptors T1R2 and T1R3 is responsible [74].

Hindgut Hypothesis

Additional and/or alternative theories of glucose homeostasis entail the secretions of putative peptides determined by the increase glucose load in the hindgut ("hindgut theory"). According to this second theory, the early presence of undigested food in the distal small bowel stimulates the secretion of "incretin" substances, which, in turn, determines normalization of the glycemia, increases insulin production, and decreases insulin resistance. Although, once again, a single substance has not been identified, GIP and GLP-1 remain the most promising putative candidates. Initially increased GLP-1 and GIP cannot account for improved glucose tolerance, but as glucose normalizes, the action of especially GIP on insulin secretion might be restored [8].

Neuroendocrine Mechanism

Experimental models highlight a complex interplay of hormonal and neural pathways that converge and possibly interact at various levels of the gut-brain axis to regulate energy balance. Bariatric surgery procedures, including Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), influence body weight and glucose regulation via central neural circuits that are recruited by vagally mediated pathways following activation of stretch or chemoreceptors in the stomach. Gut hormones are able to exert their effects on central pathways by either acting locally on vagal endings or via the circulation [75].

Vagus Nerve

The activation of central neural circuits, downstream of vagal afferent signaling, was recently suggested to be involved in mediating satiety and glycemic control in a mouse model of RYGB. These data implicates vagal endings in sensing the elevation in gastric distension and nutrients in the roux limb to activate an anorexigenic pathway involving the nucleus tractus solitarius (NTS), lateral parabrachial nucleus, and central nucleus of the amygdala [75]. The activation of this pathway in the immediate period following RYGB is likely to be responsible for the dramatic reduction in food intake after RYGB and may also contribute to the consumption of smaller and slower meals. In addition, there is evidence supporting the reorganization of hindbrain feeding circuits following RYGB and SG. Experimental models of SG indicate

that vagal mechanisms contribute to the efficacy of the procedure and that there is a lower threshold for activation of neurons in the NTS in response to a nutrient stimulus, as demonstrated by elevated levels of Fos protein. We have also recently generated data showing increased neural activation, under fasting conditions, within the same vagal circuits. Furthermore, the extent to which vagal mechanisms are central to the reduction in appetite (and weight loss) induced by SG also remains unclear. There is no evidence of the benefits of vagotomy on the postsurgical weight loss. Several trials on LAGB and RYGB have shown no benefits on weight loss by adding a vagotomy [69, 76–79]. Nevertheless, vagally mediated mechanisms seem to have a crucial role in the neuroendocrine mechanisms of RYGB and SG.

Bile Acids (BA)

Bile acids are synthesized from cholesterol in the liver. Ingestion of food causes bile acid secretion from the gallbladder through the common bile duct to the duodenum. Upon reaching the ileum, bile acids are transported by specific transport proteins to the portal circulation for recycling back to the liver.

The two primary bile acids produced by the liver in humans are cholic acid (CA) and chenodeoxycholic acid (CDCA). Bile acids undergo chemical modification through conjugation in the liver and dehydroxylation by gut bacteria [80]. Bile acids also function as a ligand for a specific nuclear transcription factor, the farnesoid X receptor (FXR), which forms a heterodimeric complex with retinoic X receptor-α (RXR-α) that binds to an inverted repeat sequence in gene promoters. Bile acids not only function in lipid absorption in the gut but also appear to be part of a broader physiological response to ingested nutrients that also involves glucose metabolism [81]. This is consistent with the anabolic need to store fatty acids as triglycerides, which requires a glycerol-3-phosphate backbone that is derived from glucose. The effects of bile acids on the glucose metabolism might be mediated by the activation of the L cells via bile acid-TGR5 (G protein-coupled bile acid receptor) and FXR signaling [86]. When recognized by TGR5 and FXR-α receptor in the liver, bile acid induces liver glycogen synthesis, inhibits gluconeogenesis, ameliorates body's insulin sensitivity, and controls glucose metabolism. FXR−/− mice exhibit peripheral insulin resistance, reduced glucose disposal, and decreased adipose tissue and skeletal muscle insulin signaling, and, conversely, activation of FXR by the agonist GW4064 in insulin-resistant ob/ob mice reduced hyperinsulinemia and improved glucose tolerance. The hindgut hypothesis is based on the premise that inappropriate delivery of ingested nutrients and/or digestive juices to more distal regions of the small intestine induces a putative molecular mediator that ameliorates T2D [82]. Bile acids have been implicated as key molecules in this hypothesis. Recent work in both clinical studies and animal models supports a key role for bile acids. Systemic BA levels are elevated in patients following RYGB, suggesting an increase in BA signaling after RYGB. SG has been shown to modify the expression of certain hepatic genes involved in the metabolism of bile acid [83–85]. Furthermore, recently FXR has been shown to be required for the antidiabetic effect of SG in mice [28]. Also SG resulting in resolution of T2D seems to contradict the hindgut hypothesis, inappropriate delivery of nutrients and digestive components to the distal intestine hypothesis. However, gastric transit is substantially increased in SG, expediting delivery through the duodenum into the distal intestine. The binding of bile acids with the nuclear receptor FXR (farnesoid X receptor) has been associated with positive alterations of the feeding behavior (repression of rebound hyperphagia), improved glucose tolerance, and likely alteration of the gut flora in post-vertical sleeve gastrectomy mice, as opposed to post-VSG FXR knockout counterpart [87]. Further delineation of the molecular mechanisms underlying these beneficial effects could provide target for novel, less invasive, and efficient treatments.

Gastrointestinal Microflora

The composition of the gastrointestinal microflora established during the first year of life influenced by a variety of environmental and metabolic factors is relatively stable during adulthood. However, the adult colon has rich microbial diversity resulting from the estimated 1000–36,000 different bacterial species contained within its lumen [103]. This diverse bacterial population contains perhaps 100 times more genes than the human genome [104]. The coexistence of the intestinal microbiota is essential for several host functions, such as vitamin synthesis. Recently additional links between gut flora and the metabolism have been discovered. Instrumental in this process is the fact that both mouse and human microbiota are prevalently populated by the same bacterial species: *Bacteroidetes* and *Firmicutes*. Comparisons of the distal gut microbiota in genetically obese mice and their lean littermates have revealed that changes in the relative abundance of the two dominant bacterial divisions, the *Bacteroidetes* and *Firmicutes*, are associated with the level of adiposity [105–107]. Specifically, obese mice have a significantly higher level of *Firmicutes* and lower levels of *Bacteroidetes* compared with their lean counterparts [108]. Similar results have been established in humans [107]. Furthermore, biochemical analyses have indicated that such shifts in microbial community structure are associated with an increased efficiency in energy harvest in obese individuals

from a given caloric load; these findings suggest that the gut microbiota may be a significant contributor to an individual's energy balance.

It has been well documented that weight loss is of great benefit in obese patients with type II diabetes mellitus (T2DM), often eliminating the need for pharmacologic intervention to treat insulin resistance [109, 110]. It has also been established that diet-induced weight loss in humans has a marked effect on gut microbial ecology—shifting the gut microbial community composition toward that seen in lean individuals [107]. Intriguingly, experimental alteration of intestinal flora in genetically obese mice results in weight loss independent of improvement of glycemia [111]. The division-wide change in microbial ecology that has been associated with obesity suggests that the obese gut microbiota may play an important role in the morbidity associated with obesity, and its modification might be responsible for the resolution of some comorbidities.

Changes in the composition of the gut microflora after RYGB are a potential contributor to both weight loss and comorbidity resolution. However, this mechanism has received little attention. Zhang et al. demonstrated that the *Firmicutes* were decreased in three gastric bypass patients compared to normal-weight and obese individuals [112]. Meanwhile, Woodard et al. directly manipulated the gastrointestinal microbiota using a *Lactobacillus* probiotic agent following gastric bypass [113]. They showed that the probiotic group had greater weight loss than matched controls. In a mouse model, SG is associated with changes in the gut microbiome at 1 week and persists 1 month following surgery. The identified increases in members of the Enterobacteriaceae, Enterococcaceae, and Porphyromonadaceae families correlate with reduced weight. *Enterobacteriaceae*, within *Proteobacteria*, has been observed to increase following SG and RYGB in mice by others as well. This parallels observations in humans following RYGB. These experiments suggest that the gastrointestinal microbiota may play a significant role in human energy homeostasis. Although it is clear that microbiota play important roles in many aspects of energy metabolism, further work is needed to characterize and identify the metabolic contribution of gut microbial changes associated with SG.

Adipose Tissue

The excessive peripheral deposition of fat has been associated with peripheral and hepatic insulin resistance [88]. Furthermore, it is well known how the visceral fat constitutes a true hormone-producing substrate. Consequently, obese patients present increased levels of pro-inflammatory cytokines such as TNF, interleukin-6, and leptin and reduced levels of anti-inflammatory hormones such as adiponectin [89].

The impact of bariatric surgery on the inflammatory markers, specifically which inflammatory markers are closely associated with changes in obesity and improvements in insulin sensitivity, needs further delineation. The endocrine role of the adipose fat has been well established [90]. Among the multiple adipokines described, omentin-1 has been more recently described as an important modulator of insulin sensitivity [91, 92]. Plasma omentin-1 levels and its adipose tissue gene expression are markedly decreased in obese individuals [92]. Plasma omentin-1 levels are positively correlated with both adiponectin and HDL levels and negatively with insulin resistance [92]. The omentin genes are located in the same chromosomal region associated with the development of type II diabetes [93, 94].

Leptin

A paramount contribution for the comprehension of the regulatory mechanisms between food intake and energy regulation has been the discovery of the adipokine leptin. As it stands now, levels of circulating leptin result from the contribution of two major organs, the white adipose tissue and the gastric mucosa. This hormone crosses the blood-brain barrier, and its main sites of action are the hypothalamic cells where it plays fundamental roles in the control of appetite and in the regulation of energy expenditure. At first it was considered a hormone specific to the white adipose tissue; however, recently it was found expressed by other tissues. Among these, the gastric mucosa has been demonstrated to secrete large amounts of leptin. Secretion of leptin by the gastric chief cells was found to be an exocrine secretion. While secretion of leptin by the white adipose tissue is constitutive, secretion by the gastric cells is a regulated one responding very rapidly to secretory stimuli such as food intake [95]. In general, decreased levels of leptin have been associated with increased hunger [96]. Some authors suggested a direct link between leptin and inhibition of lipogenesis and increased lipolysis. In fact, obese individuals have an increased baseline concentration of leptin, and the levels decrease after weight loss [97].

Since the reduction of leptin also leads to a reduction in energy expenditure, the maintenance of weight loss simply through diet becomes challenging [51]. The reduction of leptin has been reported in all the bariatric procedures (RYGB, LSG, LAGB), and it has been linked directly with weight loss [52]. Interestingly, post-RYGB patients who remain obese present a decreased level of leptin, suggesting mechanisms other than weight loss to explain the postoperative changes [98]. Further studies regarding the effects of bariatric surgery in the gastric mucosal leptin secretion are needed to determine the extent of its contribution to the well-established physiological mechanisms of bariatric surgery.

Table 5.3 Changes of adipocytokine after bariatric operations

	Leptin	Adiponectin	Omentin
Obese	↑	↓	↓
Post RYGB	↓	↑	↑

Adiponectin

Adiponectin is also produced by the adipose tissue, and it is related to insulin sensitivity and fatty acid oxidation [99]. Contrary to leptin, adiponectin levels are decreased in obese patients and increase with weight loss [100]. Low adiponectin levels are associated with insulin resistance and coronary artery disease [101]. After RYGB, the levels of adiponectin increase and correlate with the improved insulin sensitivity measured by HOMA-IR [98]. Furthermore, lower preoperative levels of adiponectin have been linked to greater increase in postoperative levels and increased weight loss, maybe because of enhanced fatty acid oxidation into the muscle [98]. The adiponectin-related decrease in TNF-α(alpha) has been advocated as a potential mechanism to decrease monocyte adhesion to the endothelial cells [102].

The reason for the changes of the mentioned cytokines after RYGB seems to be related mainly, but not exclusively, to the weight loss, as it has been similar for other bariatric procedures and for calorie-controlled diets [51] (Table 5.3).

β(Beta)-Cell Changes

Besides the previously mentioned gastrointestinal hormones, residual ß(beta)-cell function has been implicated as a determinant in the glycemic control after bariatric operations [114]. In fact, the rate of remission of diabetes has been linked to the patient-specific characteristics of the diabetes itself. Shorter diabetes duration, lesser degree of β(beta)-cell dysfunction (C-peptide positive), and lesser or no insulin requirements have been linked to higher chance of diabetes remission after surgery [114, 115]. Also it has been shown how, on one hand, RYGB results in an improvement of insulin sensitivity proportionally to the weight loss, but on the other hand, β(beta)-cell glucose sensitivity increases independently from it [116]. To further validate the importance of the residual ß(beta)-cell function for the remission of diabetes, some studies have shown the lack of significant benefit of RYGB in glycemic control of type I DM, in spite of similar changes of GLP-1 and weight loss as in type II DM patients [114]. It is important to note that some, and probably less convincing, evidence exists of type I DM amelioration after RYGB. In fact, in a small series of three patients, a significant and durable (8 years) improvement in glycemic control was demonstrated, suggesting other mechanism other than residual β(beta)-cell function [117]. However, the increase of GLP-1 after type I DM, although comparable with a similar increase in type II DM patients, does not determine suppression of glucagon secretion, but rather an increase [114]. This unexplained phenomenon, once again, suggests additional factors responsible for glycemic control after bariatric operations besides the degree of β(beta)-cell function. However, more recent animal studies have demonstrated pancreatic islet cell histopathological changes following RYGB showing reduced islets interstitial fibrosis, as well as regeneration and hypertrophy of beta cell mass. These findings suggest that RYGB may have a role in promoting islet regeneration. Notch signaling is an evolutionary conserved pathway of cell-cell communication and cell-fate determination during embryonic development and tissue homeostasis. The results from previously mentioned animal studies indicate a potential role of this signaling pathway in regulating the pancreatic islet regeneration following RYGB.

End-Organ Changes

Increased Insulin Sensitivity

The beneficiary effects of bariatric surgery are evident on both the insulin secretion and the improvement of insulin sensitivity. In general, weight loss determines increases in peripheral insulin sensitivity, but this is not the only mechanism after bariatric surgery.

The most convincing evidence of increased peripheral insulin sensitivity derives from the studies on BPD. Mari et al., in fact, using the hyperinsulinemic-euglycemic clamp methodology, demonstrated significant improvement of the insulin sensitivity within the day of the procedure [118]. The data for RYGB is, instead, discordant [119–123]. No significant changes have been shown in the LAGB and LSG studies [120].

Cardiac Response to Obesity and Bariatric Surgery

The "thrifty gene hypothesis" of James Neel postulates that obesity and type 2 diabetes were an evolutionary advantage in times of starvation [124]. In modern times, the ability to continually store energy has become a major disadvantage. Obesity and the development of associated complications are multifactorial and dictated by the individual exposures which include the ones that enter the body from the environment as well as those generated in excess within the body by inflammation, oxidative stress, and metabolic dysregulation. There are specific mechanisms that the body uses in an attempt to reestablish homeostasis [125]. In obesity, the body's initial response to excess energy is to partition it into adipose tissue

to reduce the metabolic burden on its major organs such as the heart. However, when the storage capacity of adipose tissue is exceeded, energy is stored ectopically as fat in vital organs creating a lipotoxic environment in non-adipose tissue. In obesity, through environmental and subsequently intrinsic factors, there is an increased hemodynamic, neurohormonal, and metabolic load.

There is strong evidence that the deposition and also the utilization of fatty acids as source of energy by the cardiac tissue are associated with increased myocardial oxygen consumption and decreased mechanical efficiency. Such studies have helped to establish obesity as an independent predictor of increased myocardia oxygen consumption and increased cardiovascular risk [125, 126]. Just until recently it is widely recognized that bariatric surgery improves cardiac function in obese patients and also reduces the risk of cardiovascular disease. The principal mechanisms involved in the benefits of bariatric surgery, predominantly RYGB and SG, occur at a micro cellular level in the endoplasmic reticulum (ER). The ER is responsible for balancing the nutritional status of the cell, homeostasis that is vital for protein synthesis, energy storage, and continued nutrient sensing. When supplied with excess substrate, ER undergoes stress, widely associated with cardiac dysfunction and disease. In bariatric surgery, the most studied procedure in this regard is RYGB, which has shown to reduce the metabolic load and stress to the heart making it plausible that the beneficial cardiovascular effects may be mediated by the reduction of cardiac ER stress or load [127].

Gastrointestinal-Renal Axis

There is growing evidence strengthening the rationale to further explore the hypothesis of the existence of a direct communication between the gastrointestinal (GI) tract and the kidneys. This theory is based on the fact that GI hormones and peptides have shown to regulate the autocrine function of renal hormones, affecting renal function and including sodium excretion. GLP-1 is the GI hormone that has been most widely studied in this regard, demonstrating a direct and indirect natriuretic effect by targeting early tubular sodium reabsorption [128]. Moreover, along with reference to emerging data demonstrating that GLP-1 can exert direct anti-inflammatory and antioxidant effects in the kidney, we can now explain the link between the beneficial effects of bariatric surgery on hypertension resolution and kidney function improvement. Animal models provide one of the most important pieces of evidence linking the physiological mechanisms of bariatric surgery and the GI-renal axis; these are the effects of glucagon-like peptide 1 (GLP-1) and GLP-1 receptor agonists (GLP-1RAs) on renal hemodynamics. Several vascular and tubular factors result in a net reduction in afferent renal arteriolar resistance, a net increase in efferent renal arteriolar resistance and/or a reduction in hydraulic pressure in Bowman space, and thereby an increase in glomerular hydraulic pressure and single-nephron glomerular filtration rate [128, 129]. GLP-1RAs are associated with direct GLP-1R-mediated and, at least in part, nitric oxide-dependent vasodilation of the afferent renal arteriole, as well as indirect inhibition of vascular and tubular factors that are putative mediators of glomerular hyperfiltration, which is well known to be the primary event resulting in chronic kidney injury [128, 130].

In an experimental model, the integrated effect of incretin-based therapy on renal hemodynamics seems to be the result of direct vasodilative actions and inhibition of pathways of glomerular hyperfiltration, which may lead us to believe that the changes in GLP-1 following bariatric surgery may result in a similar effect on renal hemodynamics [128].

Bariatric Surgery and the Control of Blood Pressure Through the GI-Renal Axis

The kidney plays a vital role in the regulation of sodium balance and blood pressure. However, the gastrointestinal (GI) tract, which is the organ first exposed to components of food, has taste receptors and sensors for electrolytes including sodium [130]. Therefore, in addition to the kidney, there is increasing realization of the importance of the GI tract in the regulation of sodium balance and consequently on blood pressure level. Excessive sodium in the body, as a consequence of increased dietary intake and/or impaired excretion, is the most common risk factor for hypertension. In addition to renal regulation of sodium homeostasis, which has been widely described, gastrointestinal absorption and its control via GI hormones play a critical role in the control of blood pressure. Most of the electrolytes including sodium are absorbed in the small (95%) and large (4%) intestine. The intestinal absorption of fluid by GI epithelial cells occurs via active transport of (NaCl) sodium chloride. NaCl absorption occurs from the small intestine to the distal colon. The GI-derived hormones can be grouped into three classes: GI hormones, pancreatic hormones, and GI neuropeptides. According to their ability to affect sodium excretion, we can further classify these hormones and neuropeptides into two groups: a group that increases and another group that decreases sodium excretion. Of these hormones, ghrelin and GLP-1 have the strongest evidence implicating them with the beneficial effects of bariatric surgery [130, 131]. In animal models, ghrelin exerts its effect on distal nephron-promoting diuresis and renal nitric oxide production. Additionally, ghrelin also stimulates nephron-dependent sodium reabsorption. Ghrelin's direct effect in the function of renal cells consists in the reduction of mitochondrial

membrane potential, and mitochondrial-derived reactive oxygen species (ROS) ameliorates angiotensin II-induced cell senescent in the renal proximal tubule cells. GLP-1 inhibits sodium uptake and facilitates natriuresis, and an animal model demonstrates the effect of GLP-1 in the brush border of proximal tubules inhibiting the sodium-hydrogen antiporter 3 (NHE3) activity and sodium reabsorption in RPT cells. Both long-term and short-term studies have shown that the blood pressure decreases in adults who underwent RYGB and SG. Compared with RYGB, sleeve gastrectomy is associated with better early remission rates for hypertension. Overall evidence suggest that this may be related to the ability of bariatric surgery to increase the plasma levels of natriuretic enterokines such as GLP-1 [130–132].

Conclusion

Although the mechanism of action of the different bariatric operations is not completely understood, multiple factors seem to play a role.

The weight loss seems only in part due to purely restrictive mechanisms. Hormonal changes stimulate anorexigenic pathways in the brain. Furthermore, the role of bile salts and the gastrointestinal microflora needs further elucidation.

Similarly the resolution of diabetes appears to be a multifactorial process. It is likely that two of the major early contributors are the increased hepatic insulin sensitivity due to caloric restriction and the improved ß(beta)-cell function secondary to increased entero-hormones caused by altered exposure of the distal small intestine to nutrients. Later changes of the glucose homeostasis are likely due to weight loss-induced improvement of peripheral skeletal muscle insulin sensitivity.

Question Section

1. Which one of the following gut hormones increases after *RYGB*?
   A. GLP-1
   B. Ghrelin
   C. GIP
   D. A + C
   E. A + B
2. Which one of the following statements is/are *TRUE* about leptin?
   A. Leptin is inversely associated with hunger.
   B. Leptin increases lipolysis and decreases lipogenesis.
   C. Leptin decreases after bariatric surgery.
   D. Leptin is directly related to energy expenditure.
   E. All of the above.

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