Mechanisms of Action of the Bariatric Procedures

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Chapter Objectives

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

Introduction

The reduction of adult and childhood obesity has been the prime subject of many recent public health campaigns. The need for these considerable efforts derives from the astounding reports of the prevalence of obesity in the US population. In fact, in spite of the relative stability of such prevalence between the years 2003–2004 and 2009–2010, more than 30 % of the adults and 17 % of the children are obese, and the actual numbers of people affected are growing rapidly [1, 2]. The increasing numbers of obese individuals have also determined a secondary epidemic of the related comorbidities, in particular the risks of diabetes and cardiovascular diseases.

Bariatric surgery is the most effective method of sustained long-term weight loss, and it has been extensively proven to ameliorate or resolve most of the associated comorbidities with severe obesity, diabetes included [3]. Traditionally the accepted mechanisms of action of the bariatric procedures were based on the concepts of restriction of calorie intake, malabsorption of nutrients, and a combination of the two. As the close interaction between diet, gut, and brain hormones become known, the mechanisms of action of these procedures, as well as their classification, have significantly changed. In fact, it has now become well recognized how the centrally regulated body weight homeostasis is profoundly influenced by hormones secreted in the intestinal tract and adipose tissue [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 is an important one but not the only of the factors involved in remission of metabolic syndrome. 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 preceding the expected weight loss [6, 7].

We here 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 the bariatric procedures in the three main categories: restrictive, malabsorptive, and combined. Although a clear understanding of all the mechanisms of action of the 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.

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Table 5.1 Potential mechanisms of action of the bariatric operations [8]

	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	+/–	+	+[b]	++	++

[b]Only related to weight loss

Potential contributors to weight loss and diabetes resolution are as follows (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].

Caloric Restriction

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 weight loss results in the short term between 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]. 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 vertical sleeve gastrectomy (VSG) has been studied in rats [28]. Similarly to what is found after RYGB, in spite of the different anatomic alterations, post-VSG 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.

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 to be 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, decrease 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]. This hypothesis is reinforced by the lack of GLP-1 postprandial changes in purely restrictive procedures, such as LAGB [38]. Also, the contact of nutrients with the proximal gut via remnant gastrectomy feedings will reverse the hyperinsulinemic hypoglycemia and the GLP-1 levels in post-RYGB patients [39]. In fact, postprandial hypoglycemia after RYGB seems to derive from the excessive insulin response on one hand and the improved peripheral insulin sensitivity on the other. The excessive postprandial insulin secretion is likely due to the enhanced GLP-1 response [40]. In fact some positive effects on the hypoglycemic syndrome have been reported with the use of GLP-1 receptor agonists (exenatide, liraglutide) [40].

Table 5.2 Characteristics of the 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)	↓↓

Finally, the accelerated gastric transit time might be responsible for the significant increase in GLP-1 after LSG [41].

Additional mechanisms to explain the GLP-1 increase are related to the inhibition of the GLP-1 degradating 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 remains controversial. 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)

This hormone is mainly secreted by the K cells of the duodenum and proximal jejunum. Its secretion is also 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 role of GIP in diabetic patients is less clear, although consistently demonstrated to be impaired [47]. Also the effects of bariatric surgery on GIP are discordant. 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 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 the bariatric procedures remains elusive.

Peptide Tyrosine Tyrosine (PYY)

Similarly to GLP-1, PYY is secreted by the L cell of the distal ileum and colon and degraded by the enzyme DPP-IV. PYY is also secreted by the brain. The secretion of PYY is proportional to the caloric density of the nutrients [49]. The main mechanism of action of PYY is the inhibition of gastric emptying and intestinal motility (ileal break). PYY also decreases appetite through direct central mechanisms [50]. The effects of PYY on glucose metabolism are indirectly determined by the insulin sensitivity changes secondary to the activation of melanocortin neurons [51]. At base line, obese individuals express lower fasting and meal-stimulated levels of PYY [33]. PYY seems to play a key role in the weight loss effects of certain bariatric operations. In fact, PYY levels are consistently and quickly increased after RYGB, BPD, and LSG, but not after LAGB [36, 52, 53]. Contrary to RYGB, though, PYY levels tend to normalize overtime in LSG patients [54]. As previously discussed for GLP-1, the premature presence of nutrients in the distal ileum and the rapid gastric transit could explain these findings [55]. Also, because of the potential decreased in gastric pH of the LSG, some authors speculated that this higher pH and less digested chyme delivered to the duodenum could contribute to the increase release of PYY [56]. The importance of PYY in the achievement of satiety and weight loss has been demonstrated in several studies [36, 57]. In fact, decreased variations of PYY after RYGB were associated with poorer weight loss or weight regain in prospective studies [36].

The key role of PYY in the post-bariatric surgery weight loss seems then to be well established.

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) [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 a potent inducer of satiety. It is normally secreted from the duodenum and proximal jejunum in response to nutrients. Additionally, CCK plays a key role in gallbladder and gastric emptying and exocrine pancreatic secretion. Unclear evidence exists 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 [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 [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]. But 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.

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 decrease 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.

Vagus Nerve

The extensive innervation of the gastrointestinal tract by the vagus nerve provides neural pathways that connect the brain with enteric cells. Some of the effects of the previously mentioned hormones are mediated by the vagus nerve [75]. As previously mentioned, vagotomy has been associated with decreased levels of ghrelin [68]. However, there is no evi-

dence 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].

Satiety-Induced Gastric Sensory Receptors

The gastric cardia has extensive vagal afferents. The intraganglionic laminar endings (IGLEs) are mechanoreceptors that lie attached to the sheath of the myenteric ganglia and are known to detect tension within the wall of the stomach. Video-manometry studies [77] in LAGB have demonstrated that the esophageal peristalsis transports the bolus of food to reach the lower esophageal sphincter, which then relaxes as this peristaltic wave approaches. An after-contraction is generated, which can maintain some of the pressure of the peristaltic wave as a part of the food bolus is passed into that small upper stomach. There is only a brief delay of semisolid food transit into the stomach below the band, and overall gastric emptying is close to normal. The upper stomach, including the area under the band, can be sensitive to these pressure mechanoreceptors from the IGLEs.

Appropriately adjusted bands generate a basal intraluminal pressure of 25–30 mmHg and after a meal can induce an immediate inter-meal satiation effect [77, 78]. This satiety effect can be attributed to the activation of the gastric sensory receptors by the distention of the small pouch [79, 80]. Another possibility is that the direct pressure or contact of the band on the gastric wall might induce satiety. Increased hunger has been correlated with fluid removal from a well-adjusted band [78]. Rapid weight gain is associated with reduced satiety and has been reported as quickly as 1–2 days after removal of the band [81].

Bile Acids

Bile salts are important regulators of the energy balance, and they might increase energy expenditure in brown adipose tissue [33]. The concentration of bile acids increases consistently after RYGB and LSG [82, 83]. This is probably due to the decreased enterohepatic circulation with a resulting increased conversion of cholesterol to bile acids. More inconsistent are the results after LAGB, with some evidence of increase, and some other showing the opposite [84, 85]. The explanation for the increase in bile salts after the latter procedures could come from an increase in endogenous cholesterol synthesis secondary to decrease intake [33]. The effects of bile acids on the glucose metabolism might be on the activation of the L cells via TGR5 receptors, causing the release of the previously mentioned hormones [86]. Also LSG has been shown to modify the expression of certain hepatic genes involved in the metabolism of bile acid [83]. The importance of these findings resides in the newly discovered role of the bile salts. In fact, besides the well-known role in facilitating the digestion and absorption of lipids, the bile acids have been recognized as true signaling molecules [87]. 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].

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 proinflammatory 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 2 diabetes [93, 94].

Leptin

Leptin is an adipocytokine secreted by the white adipose tissue, and its levels are directly related to the energy balance. In general, decreased levels of leptin have been associated with increased hunger [95]. Some authors suggested a direct link between leptin and inhibition of lipogenesis and increased lipolysis [96]. 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].

Table 5.3 Changes of some 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].

The changes of the principal *adipocytokine* before and after surgery are summarized in Table 5.3.

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 1,000–36,000 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 2 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 affect 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.

Alteration in the composition of the gut microflora after RYGB is 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. These experiments suggest that the gastrointestinal microbiota may play a significant role in human energy homeostasis.

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, recent 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.

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 mechanisms 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, 120]. No significant changes have been shown in the LAGB and LSG studies [120].

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

Questions

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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