Review Article

Physiological Principles of Bariatric Surgery: The Good and the Dark Side

Princípios Fisiológicos da Cirurgia Bariátrica: O Bom e o Vilão

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ABSTRACT

Obesity is a chronic, relapsing, and multifactorial disease arising from the complex interaction of neuroendocrine, genetic, and environmental factors. Traditional anthropometric measures, such as body mass index, inadequately capture the underlying pathophysiology of adipose tissue dysfunction and energy dysregulation. Metabolic and bariatric surgery remains the most effective and durable therapy for obesity and its metabolically related diseases; however, its benefits extend far beyond mechanical restriction and/or hypo- or malabsorption.

This review synthesizes current evidence on the physiological mechanisms underlying metabolic and bariatric surgery, focusing on how distinct procedures modulate gut–brain signaling, energy balance, and metabolic homeostasis. Key pathways influenced by metabolic and bariatric surgery—including alterations in gut hormone secretion, entero-insular axis activity, bile acid metabolism, gut microbiota composition, vagal signaling, and adipose tissue remodeling—are discussed. The review also addresses the metabolic outcomes associated with the most common surgical techniques and explores the "dark side" of bariatric surgery, encompassing dumping syndrome, post-bariatric hypoglycemia, and weight regain.

Metabolic and bariatric surgery induces systemic physiological reprogramming that transcends anatomical modification, acting primarily through neuroendocrine networks governing appetite, metabolism, and energy expenditure. A deeper understanding

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of these mechanisms is essential for optimizing procedure selection, improving long-term outcomes, and advancing the precision management of obesity as a chronic disease.

Keywords: Appetite Regulation; Bariatric Surgery/adverse effects; Bariatric Surgery/methods; Dumping Syndrome; Gastrointestinal Hormones Obesity/surgery; Hypoglycemia/etiology; Postoperative Complications

RESUMO

A obesidade é uma doença crónica, recidivante e multifatorial, resultante da complexa interação entre fatores neuroendócrinos, genéticos e ambientais. As medidas antropométricas tradicionais, como o índice de massa corporal, avaliam de forma inadequada a fisiopatologia subjacente à disfunção do tecido adiposo e à desregulação energética. A cirurgia bariátrica e metabólica continua a ser o tratamento mais eficaz e duradouro para a obesidade e suas doenças metabólicas associadas; contudo, os seus benefícios estendem-se muito além da restrição mecânica e/ou da hipoabsorção.

Esta revisão sintetiza as evidências atuais sobre os mecanismos fisiológicos subjacentes à cirurgia bariátrica e metabólica, com foco em como diferentes procedimentos modulam a comunicação trato gastrointestinal–cérebro, o balanço energético e a homeostase metabólica. São discutidas as principais vias fisiológicas influenciadas pela cirurgia bariátrica e metabólica, incluindo alterações na secreção de enterohormonas, na atividade do eixo enteroinsular, no metabolismo dos ácidos biliares, na composição da microbiota intestinal, na sinalização vagal e na remodelação do tecido adiposo. A revisão também aborda os desfechos metabólicos associados às técnicas cirúrgicas mais comuns e explora o "lado sombrio" da cirurgia bariátrica, que inclui a síndrome de *dumping*, a hipoglicemia pós-bariátrica e o reganho ponderal.

A cirurgia bariátrica e metabólica induz uma reprogramação fisiológica sistémica que transcende a modificação anatómica, atuando principalmente através de redes neuroendócrinas que regulam o apetite, o metabolismo e o gasto energético. Uma compreensão mais profunda desses mecanismos é essencial para otimizar a seleção do procedimento, melhorar os resultados a longo prazo e avançar na gestão personalizada da obesidade enquanto doença crónica.

Palavras-chave: Cirurgia Bariátrica/efeitos adversos; Cirurgia Bariátrica/métodos; Complicações Pós-Operatórias; Hipoglicemia/etiologia; Hormonas Gastrointestinais; Obesidade/cirurgia; Regulação do Apetite; Síndrome de Esvaziamento Rápido

INTRODUCTION

Obesity is a chronic, multifactorial disease characterized by excess adiposity that impairs health. Although body mass index (BMI) is widely used to assess adiposity, it does not reflect fat distribution or composition and may misclassify individuals. It is defined as a BMI ≥30 kg/m², or ≥25–27 kg/m² in high-risk groups such as Asians, who exhibit greater cardiometabolic risk.[1] Beyond anthropometry, obesity is now recognized as a progressive, relapsing neurobehavioral disorder in which adipose tissue dysfunction drives adverse metabolic, biomechanical, and psychosocial outcomes.[2] Dysregulated adipokine secretion (reduced adiponectin, elevated leptin and resistin) drives systemic inflammation and metabolic dysfunction, predisposing to type 2 diabetes (T2D), cardiovascular disease (CVD), non-alcoholic fatty liver disease, cancer, and premature mortality.[3] Understanding these consequences requires examining the underlying pathophysiology.

Obesity arises from a persistent imbalance between energy intake and expenditure, shaped by complex neuroendocrine, genetic, and environmental factors. At its core, obesity is a disease of the brain, with the hypothalamus serving as the central hub of energy regulation, integrating homeostatic feeding, essential to meet physiological demands, with hedonic feeding, driven by reward and pleasure. This central regulation is further modulated by peripheral inputs from the gut, adipose tissue, pancreas, liver, and other organs, through hormones such as leptin, ghrelin, insulin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), peptide YY (PYY), cholecystokinine (CCK), and oxyntomodulin (OXM). When hedonic signals override homeostatic control, sustained excess energy intake ensues, culminating in obesity.[4]

Within this framework, the concept of a body fat or metabolic "setpoint" describes the body's tendency to autoregulate fat

and weight within a narrow range.[4,5] This regulation depends largely on leptin and gut hormone signaling. Impairments in these pathways, such as leptin resistance, shift the setpoint upward, altering appetite control and promoting excess energy intake. While the individual baseline setpoint has a genetic component, environmental factors may drive adaptive changes. Leptin resistance promotes adipose tissue expansion until leptin levels are restored, establishing a higher setpoint at which weight stabilizes. This mechanism helps explain the limited long-term efficacy of caloric restriction diets.[6]

Thus, diet and exercise address only part of energy balance, and the negative energy state they induce is transient until homeostasis resets at the prevailing setpoint. Effective long-term obesity management therefore, requires resetting the metabolic setpoint to a lower level, enabling the maintenance of body fat mass and body weight with minimal fluctuation. In this context, therapeutic strategies are increasingly targeting central and peripheral signaling pathways to reshape physiological responses.[7]

Among available strategies, metabolic and bariatric surgery (MBS) remains the most effective obesity treatment. By inducing anatomical alterations that restrict food intake, accelerate intestinal transit, modify nutrient absorption, and modulate gut hormone secretion, MBS exerts profound effects on appetite regulation, glucose homeostasis, and systemic inflammation, leading to sustained weight loss (WL) and improvement or resolution of multiple obesity-related diseases. Compared with lifestyle and pharmacologic interventions, it achieves greater and more durable WL, higher rates of remission of metabolic diseases, and reduced all-cause mortality.[8]

Since 2022, the American Society of Metabolic and Bariatric Surgery (ASMBS) and the Federation for the Surgery and Other Therapies for Obesity (IFSO) have recommended MBS for adults with a BMI ≥35 kg/m², or ≥30 kg/m² in the presence of metabolic disease. Lower BMI thresholds are advised for Asian populations, and MBS may also be considered in appropriately selected children and adolescents.[9]

According to the latest IFSO global registry report, sleeve gastrectomy (SG) is the most performed procedure, followed by Roux-en-Y gastric bypass (RYGB) and one-anastomosis gastric bypass (OAGB). Other procedures, including biliopancreatic diversion (BPD) with or without duodenal switch (BPD/DS), single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S), and endoscopic approaches, account for only a small proportion of the total.[10]

Although MBS is broadly effective, different techniques engage distinct mechanisms that may confer specific benefits to different patient profiles. Tailoring the procedure to individual physiological and clinical characteristics may therefore optimize outcomes, underscoring the paramount importance of understanding the physiological mechanisms underlying MBS. This review provides an updated synthesis of current evidence on these mechanisms, highlighting how surgical interventions reshape metabolic regulation and contribute to WL and disease remission.

1. RESTRICTION, HYPOABSORPTION METABOLIC EFFECT—ARE THERE BOUNDARIES?

MBS have been classified into three main types- restrictive, hypoabsorptive, and combined- according to their presumed predominant mechanism of action. Restrictive procedures reduce gastric reservoir capacity to limit food intake, whereas hypoabsorptive procedures decrease the functional length of the small intestine. Adjustable gastric band (AGB) and SG are representative examples of restrictive surgeries, and the historic jejunoileal bypass or BPD are examples of hypoabsorptive surgeries. RYGB remains the prototypical example of the combined group.[11]

Although this categorization has been useful for systematizing the surgical procedures, studies over the past two decades have demonstrated that the benefits of MBS cannot be fully explained by mechanical restriction or hypoabsorption alone.[12] In fact, MBS exerts a significant metabolic effect, defined as a positive impact on metabolic disorders, which appears to begin even before the significant WL occurs.[13] Pories *et al*[14] first reported rapid normalization of glycemia after RYGB in patients with T2D, while Scopinaro demonstrated remission of T2D, dyslipidemia (DL), and hypertension (HT) following BPD.[15] Notably, this effect is not limited to procedures with a hypoabsorptive component, as SG was also associated with T2D remission in 60.8% of the patients.[16]

Thus, MBS involves a complex interplay of mechanisms beyond mere restriction and hypoabsorption and is better viewed as a continuum rather than within discrete categories.

2. PHYSIOLOGIC PRINCIPLES OF BARIATRIC SURGERY

2.1. GUT HORMONES

Gut hormones are key mediators of the metabolic and WL effects of MBS. Secreted by regionally specialized enteroendocrine cells (EEC), they integrate nutrient and neural signals to regulate appetite, satiety, and glucose homeostasis.[17]

Ghrelin, secreted mainly by X/A-cells in the gastric fundus, promotes hunger and increases glucagon secretion; unlike diet-induced WL, MBS consistently lowers circulating levels.[18] In contrast, nutrient-stimulated hormones such as CCK, PYY, GLP-1, and OXM exert anorexigenic and insulinotropic effects. CCK, released from I-cells in the proximal small intestine in response to amino and fatty acids, slows gastric emptying and enhances GLP-1 secretion. GLP-1, together with PYY and OXM, is secreted from L-cells primarily in the distal small intestine following nutrient stimulation. These peptides stimulate insulin, suppress glucagon, and reinforce satiety signaling, thereby contributing to glycemic control and reduced food intake.[19]

GIP, secreted by proximal K-cells, regulates insulin and glucagon in healthy individuals but its effects are blunted in T2D.[20] Neurotensin (NT), secreted from ileal N-cells after exposure to fats and bile acids, exerts anorexigenic effects and rises markedly after bypass procedures.[21,22]

Anatomical rearrangements following MBS distinctly modulate gut hormone secretion. Both RYGB and SG induce an increased density and activity of EEC,[23,24] contributing to elevated anorexigenic and insulinotropic hormone levels. In RYGB, this effect is influenced by limb length, with EEC upregulation particularly marked beyond 200 cm of the small intestine—a segment enriched in L-cells responsible for GLP-1 and PYY secretion.[25,26]

2.2. APPETITE REGULATION AND GUT-BRAIN AXIS

Appetite regulation is tightly controlled by the gut-brain axis, a bidirectional communication network integrating neural, hormonal, and metabolic signals between the gastrointestinal tract and the central nervous system, particularly the hypothalamus. Gut hormones regulate energy homeostasis through two complementary mechanisms: a direct action on hypothalamic neurons controlling hunger and satiety, and an indirect action mediated by afferent vagal signaling that transmits peripheral metabolic cues to the central nervous system.[27]

At the central level, specific hypothalamic nuclei mediate these peripheral signals to coordinate feeding behavior. The arcuate nucleus (ARH) contains two distinct neuronal populations with opposing effects on appetite control: anorexigenic proopiomelanocortin (POMC) neurons, which suppress food intake, and orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) co-expressing neurons, which stimulate feeding.[28]

Ghrelin, secreted primarily from the empty stomach, activates hypothalamic GABAergic pathways, increasing the expression of NPY and AgRP and thereby promoting food intake. In contrast, nutrient-induced gut hormones such as CCK, PYY, and GLP-1, together with mechanical signals arising from gastric distension, exert anorexigenic effects by stimulating POMC neurons and inhibiting orexigenic signaling. The integration of these hormonal and neural inputs maintains a finely regulated balance between hunger and satiety, as well as between homeostatic and hedonic feeding.[28,29]

MBS profoundly alters gut hormone dynamics, characterized by marked ghrelin suppression, particularly after SG, and increased secretion of GLP-1, PYY, and CCK, which enhance satiety and promote durable WL.[29]

2.3. FOREGUT AND HINDGUT HYPOTHESIS

In a meta-analysis Buchwald *et al* reported that all bariatric procedures (AGB, RYGB, gastroplasty, and BPD/DS) improve metabolic disorders, though to varying degrees.[30] Subsequent studies have shown that procedures with a bypass component lead to earlier and weight-independent improvements in glucose and insulin homeostasis, while AGB achieves similar benefits more gradually and in proportion to WL.[31,32] These findings support the involvement of weight-independent mechanisms, with the foregut and hindgut hypotheses proposed to explain these effects through incretin modulation.

The foregut hypothesis proposes that exclusion of the duodenum and proximal jejunum prevents the secretion of a putative diabetogenic "anti-incretin" signal. This idea was first introduced and tested by Rubino, where duodenal-jejunal bypass (DJB) in nonobese diabetic mice led to improvements in glucose metabolism.[33] However, the exact molecular "anti-incretin" signal remains unknown, and clinical studies of DJB in humans have reported only modest rates of T2D remission.[34]

The hindgut hypothesis posits that rapid delivery of undigested nutrients to the distal intestine stimulates L-cell secretion, particularly GLP-1 and PYY. This theory was proposed by Cummings in 2004.[35] Subsequent animal and clinical studies supported this hypothesis.[36,37]

The relative contribution of each hypothesis to RYGB outcomes remains uncertain. In healthy mouse models, RYGB was compared with pre-duodenal ileal transposition, where both procedures elicited the hindgut effect, but only RYGB incorporated the foregut component. Despite comparable GLP-1 levels, RYGB induced greater GIP secretion and β-cell

mass expansion, suggesting that both mechanisms jointly mediate the surgery's metabolic benefits.[38] This finding is consistent with evidence that dual GIP/GLP-1 receptor co-agonists produce greater reductions in body weight and HbA1c than GLP-1 receptor agonists alone.[39]

The mechanisms underlying MBS extend beyond the classical foregut and hindgut theories. SG, once viewed as purely restrictive, also exerts a hindgut effect by accelerating nutrient transit and stimulating L-cell secretion.[40] Conversely, BPD/DS achieves superior glycemic control through mechanisms largely independent of GLP-1, as its secretion requires nutrient absorption.[41] Transit bipartition (SG-TB) and single-anastomosis sleeve-ileal bypass (SASI), which create dual nutrient pathways, are under evaluation and may further refine these mechanistic models.

2.4. GLUCOSE METABOLISM AND DIABETES RESOLUTION

While WL improves insulin resistance and β-cell function,[42] MBS adds entero-insular benefits, yielding up to sixfold higher T2D remission rates than non-surgical therapy.[43]

Both RYGB and SG elicit postprandial hyperinsulinemia, more pronounced after RYGB, whereas hypoabsorptive procedures such as BPD/DS attenuate glucose and insulin excursions, suggesting incretin-independent antidiabetic effects driven by enhanced insulin sensitivity.[44]

A 2014 meta-analysis found long-term remission (>5 years) rates of 99.2% for BPD/DS, 75% for RYGB, 58.2% for SG, and 24.8% for AGB.[45] A 2019 network meta-analysis including only RCTs suggested higher remission after OAGB (86.1%) than after BPD/DS (73.9%), RYGB (64.1%), or SG (52.4%), although this finding was limited by the small number of OAGB trials.[46] Later analyses with larger cohorts reported no significant differences between OAGB and RYGB.[47]

RYGB variants, namely those with longer BPL (200 cm), have been associated to a higher remission rates than standard RYGB.[48] Among other techniques, SADI-S demonstrates remission rates of 81.2%,[49] while SASI shows rates ranging from 88.3[50] to 96.4%.[51]

2.5. LIMB LENGTH INFLUENCE

Small bowel length (SBL) varies considerably among individuals, with reported values ranging from about 200 cm to over 1100 cm, and more recent studies indicating an average of approximately 690 cm.[52] This variability has important clinical implications, as many MBS involve bypassing substantial segments of the intestine. The use of standardized, non-individualized limb lengths may result in a short absorptive bowel in some patients (3% of females and 2% of males have SBL < 400 cm), or, conversely, in suboptimal outcomes in those with longer SBL (SBL >800 cm in 15% of males).[52]

In RYGB, over 85% of bariatric surgeons use standardized lengths for the BPL and alimentary limb (AL), while fewer than 18% measure the entire SBL.[53] Consequently, the common limb (CL) length—and therefore the total alimentary limb length (TALL, defined as AL + CL)—remains unknown in most studies.[54] A systematic review evaluating TALL in RYGB concluded that reducing TALL by increasing the BPL has a greater impact on WL than extending the AL.[54] Beyond weight outcomes, a 200 cm BPL has been associated with superior metabolic effects, including sustained glycemic improvements and higher long-term T2D remission.[55] These benefits may be partly explained by the increased density of L-cells observed beyond 200 cm of the small bowel.[23,26] CL becomes critical when shortened, particularly after distalization for failed RYGB, as excessive reduction is associated with marked hypoabsorption and nutritional deficiencies. To minimize this risk, a TALL of at least 300 cm with a CL length of 150 cm, is generally recommended.[56]

In SADI-S the TALL corresponds to the CL, making its minimum length crucial to avoid protein malnutrition. Indeed, adaptations in limb length have been introduced following the need for revisional surgery due to hypoproteinemia, with reported rates of 14% for a 200 cm CL, 5% for 250 cm, and 0% for 300 cm.[57] Although SADI-S and BPD/DS share the same TALL, they differ anatomically: in BPD/DS, biliopancreatic secretions meet nutrients more distally, resulting in a shorter CL. This anatomical difference accounts for the greater WL and higher T2D remission rates in BPD/DS, particularly in patients with BMI ≥55 kg/m^2,[58] but also increases the risk of essential amino acid malabsorption and nutritional deficiencies compared with SADI-S.[59]

A higher excluded bowel ratio (BPL/SBL) correlates with greater WL after RYGB,[60] SADI-S,[61] and OAGB.[62] However, standardized limb lengths yield variable ratios across individuals,[62,63] raising concerns of under- or over-treatment. Consequently, several groups advocate tailoring limb lengths to measured SBL.[64,65] Although short-term outcomes appear comparable,[66] individualized configurations may mitigate nutritional deficiencies despite longer BPL.[67]

2.6. HORMONAL PROFILES BY BARIATRIC TECHNIQUE

The impact of MBS on incretin dynamics varies according to the procedure. Despite substantial WL, AGB does not affect ghrelin, GIP, and GLP-1 levels.[68]

As expected, given the gastric fundus as the main site of ghrelin production, SG is associated with a marked reduction in ghrelin levels. Similar changes are observed in other procedures incorporating SG, such as BPD/DS and SADI-S, and can likely be extrapolated to SG-TB and SASI. Although SG preserves the pylorus, several studies suggested that gastric emptying accelerates after surgery, potentially delivering more undigested nutrients to the small bowel, thereby stimulating EEC. This is suggested by the increases in postprandial GLP-1 and PYY. Enhanced postprandial CCK release after SG, which may further contribute to GLP-1 secretion, is consistent with the absence of bypassed proximal bowel. In contrast, GIP levels do not differ from controls.[69,70]

RYGB induces a more pronounced GLP-1 and PYY response compared with SG,[71] likely due to the immediate pouch emptying into more distal small bowel segments.[72] Ghrelin dynamics also differ from SG, reflecting the presence of the gastric remnant.[73] As anticipated with duodenal and proximal jejunal exclusion, CCK secretion increases less than after SG.[73] GIP levels after RYGB are inconsistent; however, a recent meta-analysis reported overall declines in both fasting and postprandial levels, particularly among patients with T2D.[74]

OAGB seems to yield similar postprandial secretions of ghrelin, GLP-1, GIP and PYY when compared with RYGB.[75]

Hypoabsorptive procedures such as SADI-S and BPD/DS are characterized by enhanced postprandial secretion of GLP-1 and PYY. However, this hormonal response is attenuated in BPD/DS, accompanied by lower postprandial excursions of glucose, insulin, C-peptide, and glucagon, findings consistent with its shorter CL.[76] Furthermore, evidence of reduced amino acid absorption, decreased circulating bile acid levels, and elevated NT concentrations reinforces the more pronounced hypoabsorptive component of BPD/DS.[77]

Recent comparison between standard-RYGB (100 cm BPL), metabolic-RYGB (200 cm BPL), SADI-S, and BPD/DS showed that standard-RYGB was associated with the greatest glycemic variability and the most pronounced insulin secretion. In contrast, insulin responses were intermediate after metabolic-RYGB and SADI-S, and least evident after BPD/DS. Postprandial GLP-1 secretion was greater after both RYGB variants, being more pronounced in metabolic-RYGB, consistent with the distribution of L-cells, while GIP levels were highest after standard-RYGB, reflecting proximal stimulation of K-cells.[77]

2.7. OTHER FACTORS

2.7.1. BILE ACIDS

Bile acids are key mediators of gut–brain signaling after MBS, with circulating levels rising significantly following both RYGB and SG. The mechanisms underlying this increase are not fully understood. In RYGB, anatomical diversion of bile flow to the mid-jejunum may explain the more consistent and pronounced elevation compared with SG, while lipid malabsorption may also induce compensatory upregulation of bile acid synthesis. Functionally, bile acids activate the farnesoid X receptor (FXR) and the G protein–coupled receptor TGR5, promoting GLP-1 and PYY secretion, enhancing insulin sensitivity, and modulating systemic energy metabolism. They also support gastrointestinal barrier integrity through antimicrobial activity and FXR-mediated induction of antimicrobial genes.[78,79]

Fibroblast growth factors (FGFs) further integrate bile acid signaling with hepatic metabolism and central appetite regulation. FGF19, secreted in the ileum via FXR activation, rises after RYGB, suppresses hepatic gluconeogenesis, and may modulate hypothalamic appetite pathways. FGF21, produced mainly in the liver, also increases postoperatively and is associated with improved lipid metabolism, higher energy expenditure, and regulation of feeding behavior. Meta-analyses confirm consistent postoperative increases in both FGF19 and FGF21, though heterogeneity in study design and methodology limits precise interpretation of their roles.[80,81]

Overall, the contribution of bile acids to WL remains unclear. Current evidence suggests they act primarily through indirect anorectic effects mediated by GLP-1 and PYY, while FGF19 may additionally modulate hypothalamic AgRP/NPY neurons.

2.7.2. GUT MICROBIOTA

Beyond hormonal adaptations, MBS induces marked alterations in gut microbiota, which influence appetite regulation and energy homeostasis. Distinct procedures produce specific microbial changes reflecting their anatomical modifications, with RYGB showing the most pronounced effects.[81]

In both humans and rodents, the microbiota is dominated by *Firmicutes* and *Bacteroidetes*, whose relative abundance is linked to obesity, typically with a higher *Firmicutes/*

Bacteroidetes ratio in obese phenotypes. MBS consistently increases microbial diversity, enriches taxa such as *Akkermansia muciniphila*, and modifies the *Firmicutes*/*Bacteroidetes* ratio. These shifts may affect host metabolism via several pathways: short-chain fatty acid production stimulating GLP-1 secretion through free fatty acid receptor-2; modulation of bile acid metabolism; and altered signaling to EEC. Disruption of arginine and tryptophan metabolism may also influence hypothalamic neuropeptide expression and peripheral hormone levels. Increased *Bacteroidetes* abundance has been associated with reduced inflammation, improved glucose control, and WL, while *Akkermansia muciniphila* correlates with enhanced insulin sensitivity and T2D remission.[81-83]

Although causality is difficult to establish, fecal microbiota transplantation supports a contributory role. In a study by Groot et al., transplanting fecal samples from RYGB patients with metabolic syndrome into nonsurgical recipients led to trends toward improved insulin sensitivity, contrasting with declines observed after microbiota transfer from nonsurgical donors, although differences were not statistically significant.[84]

2.7.3. VAGUS NERVE

In parallel with hormonal adaptations, neural remodeling within the gut–brain axis reinforces postoperative changes in feeding behavior. The parasympathetic nervous system, particularly the vagus nerve, serves as a conduit for afferent satiety signals, relaying gut hormone secretion, nutrient content, and visceral distension to central appetite-regulating circuits. Vagal afferents express receptors for CCK, GLP-1, and leptin, integrating peripheral inputs that suppress food intake, limit weight gain, and reduce adiposity.[85]

RYGB frequently induces partial or complete gastric vagal denervation. Rather than impairing satiation, this may alter viscerosensory pathways and central processing, resulting in persistent or exaggerated satiety, termed "phantom satiation" by Gautron.[86] Overall, MBS influences vagal function in a procedure-dependent manner, through both direct neural remodeling and indirect neuroendocrine modulation, collectively reshaping the gut–brain axis to support WL and metabolic improvements.

2.7.4. ADIPOSE TISSUE

Adipose tissue is a heterogeneous organ composed of adipocytes, fibroblasts, endothelial and immune cells, and adipocyte progenitors. Beyond energy storage, it functions as an endocrine organ, secreting adipokines, batokines, lipokines, microRNAs, and inflammatory cytokines.[87] Among these, leptin and adiponectin are the most studied. Leptin suppresses food intake by activating POMC neurons in the ARH and inhibiting AgRP/NPY neurons. In obesity, elevated leptin levels are accompanied by low-grade inflammation and leptin resistance, impairing satiety signaling.[88]

Adiponectin shows an inverse relationship with fat mass: its circulating levels decline in obesity but increase with WL, restoring concentrations closer to those of lean individuals. Higher adiponectin enhances insulin sensitivity and reduces hepatic glucose production, underscoring its metabolic relevance.[89]

After MBS, adipose tissue mass declines markedly, lowering circulating leptin. This reduction alleviates inflammation, restores leptin sensitivity, and is consistently associated with sustained adiponectin increases after both RYGB and SG. Together, these changes contribute to appetite suppression, improved insulin sensitivity, and cardiovascular protection.[89]

3. DARK SIDE OF BARIATRIC SURGERY

3.1. DUMPING SYNDROME AND POST-BARIATRIC HYPOGLYCEMIA

Dumping syndrome, traditionally termed early dumping, encompasses a constellation of gastrointestinal and vasomotor symptoms occurring within the first hour after food intake. It is a well-recognized adverse effect of upper gastrointestinal surgery and is particularly common after bariatric procedures, with an average incidence of ~15%, though higher rates have been reported depending on diagnostic criteria. Rapid gastric emptying plays a central role in its pathophysiology: partially digested food enters the small intestine, creating a hyperosmolar environment that drives fluid shifts. Symptom severity varies among surgical techniques according to pyloric preservation and vagal integrity, which modulate gastric emptying and accommodation. Even within the same procedure, differences in pouch and gastrojejunal calibration, may influence gastric emptying dynamics.[90]

The vasomotor component of early dumping remains incompletely understood, as relative hypovolemia from fluid shifts does not fully account for these symptoms; fluid restoration does not prevent their occurrence. Stimulation of intestinal L-cells by hyperosmolar chyme triggers a marked GLP-1 release, contributing to vasomotor manifestations via sympathetic activation and catecholamine secretion. Additional vasoactive mediators—such as NT and vasoactive intestinal peptide, both elevated after surgery—may further promote splanchnic vasodilation, resulting in hypotension and hemoconcentration.[90,91]

Although dumping syndrome is an undesirable consequence of MBS, the unpleasant symptoms induced by rapid absorption of refined carbohydrates often promote favorable dietary behavior, as patients tend to avoid such foods. The same gut hormones involved in dumping—primarily GLP-1 and PYY—also enhance satiety via the gut–brain axis and improve glucose metabolism in T2D. While no direct link has been demonstrated between early dumping and postoperative WL, many patients report that these aversive symptoms aid self-control and help prevent relapse into maladaptive eating patterns, albeit often at the cost of reduced quality of life.[92]

Post-bariatric hypoglycemia (PBH), also known as *late dumping*, typically occurs one to four hours after a meal and develops later in the postoperative course. It results from neurohumoral adaptations following MBS. Accelerated gastric emptying and intestinal transit shorten glucose absorption time, potentially inducing compensatory upregulation of glucose transporters. These mechanisms likely account for the higher frequency of PBH one year after surgery, particularly following RYGB compared with SG.[90,91] Enhanced glucose absorption stimulates the secretion of incretins, notably GLP-1 and GIP, driving pancreatic β-cell hyperactivity and hypertrophy and leading to hyperinsulinemic hypoglycemia.[93]

Clinically, PBH manifests with adrenergic and/or neuroglycopenic symptoms, though asymptomatic ("hypoglycemia unawareness") episodes are frequently detected during specific tests.[93] The contribution of incretins remains debated, as counter-regulatory impairment is also implicated. Studies report reduced insulin clearance, dysregulated α- and β-cell homeostasis, and decreased glucagon secretion after RYGB, leading to inadequate insulin suppression. A higher incretin-to-glucagon ratio in RYGB patients with postprandial hypoglycemia supports this mechanism.[93,94] Moreover, comparisons among bypass techniques—standard and metabolic RYGB, SADI-S, and BPD/DS—show higher insulin and C-peptide secretion after standard RYGB, underscoring the influence of anatomical configuration on incretin dynamics and insulin response.[77]

PBH exerts detrimental effects, not only through its potentially severe symptoms but also by promoting weight regain (WR). Recurrent hypoglycemic episodes stimulate compensatory caloric intake, reinforced by insulin's orexigenic action. Chronic hyperinsulinemia additionally induces leptin resistance, disrupting central leptin signaling and creating a state of "brain starvation" that enhances appetite and energy intake.[95]

3.2. WEIGHT REGAIN AND COMORBIDITIES RELAPSE

MBS remains the most effective and durable treatment for obesity and its comorbidities; however, WR remains a significant concern, highlighting the need for preventive and therapeutic strategies. Although prevalence varies depending on the definition applied, long-term data indicate that 10%–20% of patients experience clinically meaningful WR within 5–10 years, regardless of the surgical procedure.[96]

WR is a complex, multifactorial phenomenon influenced by anatomical, behavioral, psychological, metabolic, and neurohormonal factors, which are often interrelated. Anatomical alterations—such as dilation of the gastric pouch or sleeve, or enlargement of the gastrojejunal anastomosis—reduce afferent distension signaling and accelerate gastric emptying, contributing to dumping syndrome and PBH. Chronic hyperinsulinemia further stimulates appetite by lowering circulating energy substrates, enhancing glucose absorption, and reducing energy expenditure. Another anatomical cause of WR is the formation of a gastro-gastric fistula, which reestablishes duodenal passage and blunts the foregut and hindgut effects.[96,97]

WR is also part of the physiological response to WL. Caloric restriction and reduced fat mass lead to decreased leptin and incretin levels, triggering adaptive mechanisms that conserve energy by lowering resting energy expenditure and increasing appetite. In contrast to restrictive diets, MBS sustains negative energy balance despite these adaptive pressures, suggesting that its anatomical rearrangements induce hormonal and metabolic reprogramming that establishes a new, lower setpoint.[96,98]

Nevertheless, a subset of patients experiences suboptimal weight loss (SWL) or WR even in the absence of anatomical causes. Although the mechanisms remain incompletely understood, intrinsic individual factors likely contribute. Compared with successful responders, those with WR or SWL exhibit greater metabolic efficiency, lower postprandial incretin levels (PYY and GLP-1), and consequently incomplete suppression of orexigenic signals—indicating an inadequate neuroendocrine recalibration of the setpoint. In these individuals, early WL plateaus may reflect premature activation of metabolic defenses, predisposing them to WR despite adequate behavioral adherence and technically successful surgery.[98,99]

No consistent predictors of surgical failure have been identified, though SWL during the first postoperative year

is associated with a greater risk of WR and recurrence of metabolic disease.[100] Recognizing these biological predictors has important therapeutic implications, as early identification of at-risk patients—through WL kinetics, hormonal profiling, or metabolic markers—may enable timely, individualized intervention.

CONCLUSION

MBS remains the most effective obesity treatment. Far from being a mere anatomical modification that restricts food intake or absorption, it exerts complex physiological effects mediated primarily through alterations in gut hormone secretion. These changes ultimately influence hypothalamic pathways regulating appetite, energy expenditure, and long-term body weight. Additional modulation of the entero-insular axis, adipose tissue metabolism, bile acid circulation, and gut microbiota further amplifies these effects, contributing to the remission of metabolic diseases.

Unlike pharmacological therapies, MBS acts through multiple, interconnected mechanisms and targets diverse physiological systems, some of which remain incompletely understood. Nonetheless, WR following MBS reflects the chronic, relapsing nature of obesity, underscoring the need for lifelong follow-up to identify and address the underlying mechanisms.

Advancing our understanding of these processes will enable a more precise, individualized approach to obesity treatment.

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