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SURGERY FOR OBESITY AND RELATED DISEASES

Review article

Theories and concepts of physiological mechanisms in metabolic and bariatric surgery, beyond restriction and malabsorption: a narrative review

Saleha Khan, M.D.[a], Aleena Zobairi, M.D.[a], Sjaak Pouwels, M.D., Ph.D. (Mult.)[b,c,*], Alper Celik, M.D., Ph.D.[d], Surendra Ugale, M.D., Ph.D.[e], Chetan Parmar, M.B.B.S.[f,g,h]

[a]*General Medicine Program, Batterjee Medical College, Jeddah, Saudi Arabia*
[b]*Department of Surgery, University Hospital OWL of Bielefeld University – Campus Klinikum Lippe, Detmold, NRW, Germany*
[c]*Department of Intensive Care Medicine, Elisabeth-Tweesteden Hospital, Tilburg, The Netherlands*
[d]*Metabolic Surgery Clinical, Istanbul, Turkey*
[e]*Ugale Bariatrics, Kirloskar Hospital, Hyderabad, India*
[f]*Whittington Hospital, London, United Kingdom*
[g]*University College London, United Kingdom*
[h]*Apollo Hospitals Education and Research Foundation, India*

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Abstract Metabolic and Bariatric surgery (MBS) has become an essential treatment for severe obesity and associated comorbidities, particularly type 2 diabetes mellitus (T2DM), with substantial benefits in weight loss, improved glycemic control, and cardiovascular risk reduction. The International Diabetes Federation (IDF) recognizes MBS as an effective option for individuals with obesity with T2DM due to its ability to improve insulin sensitivity and lower inflammation. These surgeries induce metabolic improvements through distinct mechanisms that affect gut hormone secretion, nutrient absorption, and energy balance. These interventions modulate key gut hormones like glucagon-like peptide-1 (GLP-1), ghrelin, and leptin, which influence appetite, glucose metabolism, and fat storage. Moreover, MBS alters the gut microbiome, contributing to enhanced metabolic function and the resolution of obesity-related conditions. Theories such as the Foregut-Hindgut Hypothesis, Ileal Brake Mechanism, and Gastric Center Hypothesis further try explain these metabolic changes. Understanding these theories and the physiological alterations they provoke is crucial for optimizing patient care and advancing the future of obesity treatments, offering insights into mechanisms that go beyond simple weight loss to address complex metabolic disorders. (Surg Obes Relat Dis 2025; ■:1–11.)

Keywords: Physiology; Metabolic surgery; Bariatric surgery; Ileal brake; Metabolic theories

Metabolic and bariatric surgery (MBS) has become a very effective therapy for obesity and the comorbidities that go along with it, especially type 2 diabetes mellitus (T2DM). The International Diabetes Federation (IDF) has recognized MBS as a therapy option for people with obesity and diabetes since it lowers cardiovascular risk factors, improves glycemic management, and encourages significant weight loss. It has become a vital technique in the management of obesity and its associated health consequences due to the prevalence of these illnesses worldwide [1,2]. Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) and

* Correspondence: Sjaak Pouwels, M.D., Ph.D. (Mult.), Department of Surgery, University Hospital OWL of Bielefeld University, Campus Klinikum Lippe, Röntgenstraße 18 32756, Detmold, NRW, Germany.
E-mail address: sjaakpwls@gmail.com (S. Pouwels).

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one anastomosis gastric bypass (OAGB) are common MBS treatments that offer different strategies for improving metabolism and reducing body weight [3].

MBS has a major impact on metabolism and physiological processes, affecting several pathways that control hormone activity, glucose homeostasis, and energy balance. Weight management and metabolic health improve as a result of these operations, which cause major alterations in the body's metabolic processes. It can improve general metabolic function, lower inflammation, and increase insulin sensitivity by changing the release of gut hormones and the absorption of nutrients. T2DM and cardiovascular illnesses are 2 ailments linked to obesity that are resolved or improved by these physiological changes [4,5]. Additionally, it alters physiology and metabolism by impacting functions like energy balance, lipid metabolism, and glucose regulation. These changes enhance appetite regulation and hormonal signaling, thereby improving metabolic health and addressing obesity-related disorders [6]. This paper aims to explore the intricate metabolic and physiological mechanisms altered by MBS, providing insight into how these changes contribute to weight loss and metabolism. Understanding these mechanisms is essential for optimizing patient care and advancing the future of obesity treatments.

Methodology

A comprehensive review was conducted to investigate the metabolic and physiological changes induced by MBS, including procedures like gastric bypass, SG, and adjustable gastric banding. The search was designed to identify relevant studies on the effects of these surgeries on weight loss and associated metabolic alterations. Initially, a systematic search was performed on 5 scientific databases: PubMed, Google Scholar, Cochrane, OVID, and Embase until March 2025. Relevant keywords and MeSH terms were used, including "metabolic surgery," "bariatric surgery," "gastric bypass," "sleeve gastrectomy," "adjustable gastric banding," "gut hormones," "glucose metabolism," "insulin sensitivity," "microbiome," and "weight loss," "foregut-hindgut hypothesis," and "ileal brake."

Both preclinical and clinical studies were considered for review, including randomized controlled trials (RCTs), observational studies, and meta-analyses. A total of 2000 studies were initially identified. After applying inclusion and exclusion criteria, 150 studies were shortlisted for detailed analysis. These studies were reviewed for their findings on the mechanisms of metabolic changes, including alterations in gut hormones (e.g., ghrelin, leptin, glucagon-like peptide-1 (GLP-1)), glucose metabolism, insulin sensitivity, appetite regulation, fat storage, and the microbiome's role in enhancing metabolic outcomes postsurgery. The selected studies were evaluated for relevance, quality, and their contribution to understanding how MBS affects both metabolic function and the resolution of comorbidities. The final synthesis of the review was derived through a consensus approach among the authors. This comprehensive review aims to provide insights into the complex mechanisms triggered by these surgical procedures and their potential for advancing the treatment of severe obesity and its associated metabolic disorders.

Metabolic and physiological changes postsurgery

MBS leads to significant metabolic and physiological changes post-surgery that contribute to weight loss and the improvement of obesity-related comorbidities. These changes are both weight-dependent and weight-independent, involving various hormonal cross-talk, metabolic effects, and physiological adaptations.

Metabolic and hormonal adjustments

Hormonal adjustments following MBS play a crucial role in the metabolic improvements observed in patients. These changes primarily involve gut hormones that regulate glucose metabolism, insulin sensitivity, and appetite, contributing to the overall success of the procedure. One of the key hormones, GLP-1, is significantly elevated after MBS, improving glucose control and often leading to the remission of T2DM. Similarly, other hormones like peptide YY (PYY) also see changes, which further enhance postprandial metabolic responses. These hormonal shifts, driven by the alterations in gastrointestinal anatomy, are central to the weight loss and metabolic benefits observed in patients postsurgery [5,7,8].

A prospective study compared the effects of SG and RYGB on hormone and metabolic changes in patients. A total of 59 subjects were enrolled, with 40 undergoing RYGB and 19 undergoing SG. Blood samples were taken at various time points after a test meal to measure hormone levels. The study found that RYGB led to greater weight loss and metabolic improvements compared to SG. Specifically, RYGB showed higher mean percentage weight loss at 52 weeks, with continued weight loss over time. Hormones like PYY, GLP-1, and ghrelin were analyzed, showing potential roles in appetite regulation and glucose homeostasis. The authors highlighted the importance of gut hormones in mediating the effects of different bariatric procedures on weight loss and metabolic outcomes. Finally, the study concluded that these hormonal changes significantly improve glucose metabolism, with RYGB showing more sustained benefits for glucose homeostasis over time, which may explain its superior efficacy in weight loss and metabolic improvement compared to SG [9].

In addition to the changes in GLP-1 and PYY, the study also examined the role of other hormones, such as ghrelin and leptin, which are closely linked to appetite regulation and metabolic processes. Preoperative ghrelin levels were found to be higher in the SG group compared to the

RYGB group, although the reasons for this remain unclear. There was considerable variability in fasting ghrelin levels across individuals, with SG showing a broader range of values. Some factors reported across studies such as the assay used, which measures both active and inactive forms of ghrelin, and demographic differences like race and body mass index (BMI), may contribute to these variations. Interestingly, the study noted a significant decrease in ghrelin levels after SG, likely due to the resection of the ghrelin-secreting cells in the gastric fundus [9]. This is consistent with recent findings and may help explain the reduced appetite often seen in SG patients [8,10].

Additionally, the interplay between leptin and ghrelin is complex, and while differences in leptin levels were observed, further research is needed to clarify their role in the hormonal adaptations post-MBS and how they contribute to the differences in outcomes between RYGB and SG. In another study comparing SG, RYGB, and LAGB, it was found that ghrelin and insulin levels significantly decreased after SG and RYGB, with SG showing the most improvement in beta-cell function. High baseline ghrelin levels in SG predicted successful weight loss, suggesting its potential role in predicting outcomes after MBS [11]. However, more research is needed to validate these findings.

In addition to other hormonal changes, MBS significantly affects adipokines, myokines, and hepatokines, all of which are crucial for the metabolic improvements seen in patients with obesity as seen in Fig. 1. Studies show adipokines, such as adiponectin, leptin, and proinflammatory cytokines, are significantly modulated following surgery. Adiponectin levels increase postsurgery, promoting improved insulin sensitivity and reduced inflammation. On the other hand, leptin levels decrease in response to weight loss, correlating with a reduction in systemic inflammation. Proinflammatory adipokines like interleukin-6 (IL-6) and C-reactive protein (CRP) also show a significant decrease, reflecting a reduction in chronic low-grade inflammation. These changes in adipokine levels contribute to the overall metabolic improvements and may play a critical role in the remission of obesity-related comorbidities. Myokines such as myostatin are also affected by MBS, with a reduction in myostatin levels observed postsurgery. Myostatin is linked to insulin resistance, and its reduction helps improve muscle metabolism [12,13,14–18]. Additionally, the secretion of other myokines associated with metabolic functions, like fibroblast growth factor-21 (FGF-21) and brain-derived neurotrophic factor (BDNF), also undergoes significant changes. Although the specific roles of these myokines in the context of surgery remain a topic of ongoing research, their modulation supports enhanced metabolic health. Hepatokines such as insulin-like growth factor-binding protein 2 (IGFBP2), adropin, and sex hormone-binding globulin (SHBG) increase following surgery, contributing to better liver function and metabolic health. These hepatokines are important for regulating both liver and adipose tissue physiology and are closely linked to improvements in insulin sensitivity and overall metabolic function [19,13,20,14,15].

In the long term, MBS results in sustained improvements in various metabolic parameters. However, some markers may not return to levels typically seen in non-obese individuals, suggesting that the surgery leads to a new metabolic baseline. Despite this, the overall metabolic improvements following MBS including reduced inflammation, improved insulin sensitivity, and better control of adipokine and myokine levels are crucial for the remission of obesity-related conditions, supporting its role as a powerful therapeutic intervention for obesity and its associated comorbidities.

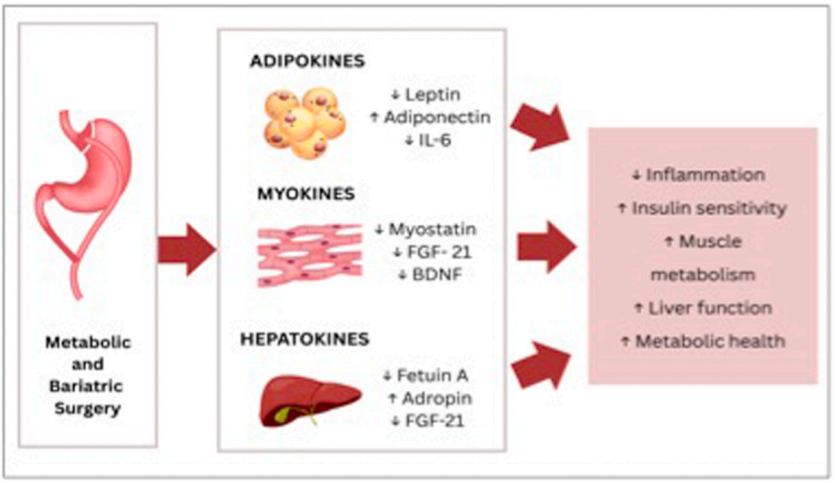

Fig. 1. Systemic hormonal modulation following bariatric surgery and its role in metabolic improvement. FGF-21 = fibroblast growth factor-21; BDNF = brain-derived neurotrophic factor; IL-6 = interleukin-6.

Bile acids and gut microbiota

MBS, particularly RYGB, OAGB, and SG, induces profound metabolic improvements beyond weight loss, largely through significant alterations in bile acid metabolism and gut microbiota composition. The changes in bile acid metabolism are critical, with studies revealing that anatomical rearrangement is a key driver [21]. For example, a study on RYGB reported fasting total plasma bile acids increased significantly from 1.08 to 2.28 μmol/L ($P = .03$), and postprandial levels rose from 2.46 to 6.00 μmol/L ($P = .01$). This rise in bile acid levels correlates with improvements in glucose metabolism, insulin sensitivity, and lipid profiles [22]. Another study even observed a bimodal increase in bile acids at 1 and 24 months post-RYGB, while another noted a sustained increase from 2.3 to 5.9 μmol/L over 5 years, coinciding with a lower BMI, greater weight loss, and reduced total cholesterol. Biliopancreatic diversion with duodenal switch (BPD/DS) demonstrated an even more substantial increase in bile acids, rising from 1.0 to 9.5 μmol/L over 5 years, whereas laparoscopic adjustable gastric banding (LAGB) produced a 49% decline in fasting bile acids (from 1.80 to .92 μmol/L) [23]. In contrast, SG procedures did not present specific bile acid data but are generally considered to induce less dramatic changes in bile acid profiles, likely due to the preservation of the normal intestinal route [24].

These bile acid alterations significantly impact metabolic outcomes, including glucose homeostasis and insulin sensitivity, due to the activation of bile acid receptors such as Farnesoid X receptor (FXR) and TGR5, which regulate glucose and lipid metabolism. The increased circulating bile acids also play a role in modulating the gut microbiota, further contributing to metabolic improvements [25,26]. Postsurgery shifts in gut microbiota composition are particularly pronounced after procedures involving extensive intestinal rerouting, such as RYGB. Studies show that RYGB leads to increased proportions of *Proteobacteria*, *Verrucomicrobia*, *Akkermansia muciniphila*, *E. coli*, and *Bacteroides/Prevotella*, alongside decreased levels of *Firmicutes*, *Lactobacillus*-related groups, and *Bifidobacterium*. These microbial changes are thought to contribute to the reduction of obesity-related inflammation and improved metabolic health. In contrast, procedures like SG and other similar surgeries typically result in only minor microbial alterations. However, a consistent pattern across various procedures is a reduction in *Firmicutes* and an increase in *Akkermansia muciniphila*, a beneficial bacterium that is associated with improved metabolic outcomes [26–28].

Moreover, a global analysis conducted in 2024 showed how MBS has shown significant impacts on the gut microbiota across studies. The gut microbiota composition is altered in response to surgery, with shifts that are closely linked to the successful outcomes of bariatric treatments. Studies have shown that specific patterns in the microbiota prior to surgery may serve as indicators of a patient's response to the procedure, and postsurgery, individuals who experience successful weight loss tend to exhibit an increase in beneficial microorganisms that positively affect host metabolism. These microbial changes contribute to the long-lasting effects of MBS, including sustained weight loss and the resolution of obesity-related comorbidities such as T2DM and metabolic associated fatty liver disease (MAFLD) [29]. Beyond the shifts in microbial composition, MBS also influences microbial function, notably by increasing the abundance of bacteria capable of converting primary bile acids into secondary bile acids. These secondary bile acids play an essential role in regulating glucose metabolism, enhancing insulin sensitivity, and improving overall metabolic health. The alterations in the microbiota following surgery contribute to an increase in the secretion of gut hormones, such as GLP-1, which enhances insulin secretion and glucose clearance, even before significant weight loss occurs [29,30].

The impact of MBS on the gut microbiota is also linked to reductions in adipose tissue, which further helps reduce systemic inflammation and improve insulin sensitivity. Long-term, these alterations in the gut microbiota contribute to improved energy homeostasis, glucose regulation, and a reduction in adiposity [30].

These findings emphasize that MBS involving substantial anatomical rearrangements, such as RYGB and BPD/DS, lead to more pronounced shifts in both bile acid profiles and gut microbiota composition compared to less invasive procedures like SG and LAGB. The combined alterations in bile acid metabolism and gut microbiota are essential for the metabolic benefits observed after MBS, contributing to enhanced glucose metabolism, insulin sensitivity, and overall metabolic health as seen in Fig. 2. As such, understanding the mechanisms underlying these changes offers promising avenues for developing non-surgical interventions that mimic the metabolic benefits of MBS, offering new therapeutic options for individuals with obesity and metabolic diseases.

Theories and mechanisms underlying surgical effects

Foregut-Hindgut hypothesis

The Foregut-Hindgut hypothesis is a theoretical framework used to explain the metabolic improvements observed after MBS, particularly in the remission of T2DM. The hypothesis is divided into two parts: the foregut hypothesis and the hindgut hypothesis. The foregut hypothesis suggests that bypassing the proximal small intestine (duodenum and jejunum) prevents the release of a diabetogenic signal, thereby improving glucose metabolism. In contrast, the hindgut hypothesis posits that the rapid delivery of nutrients to the distal intestine enhances the secretion of incretin hormones like GLP-1 and glucose-dependent insulinotropic

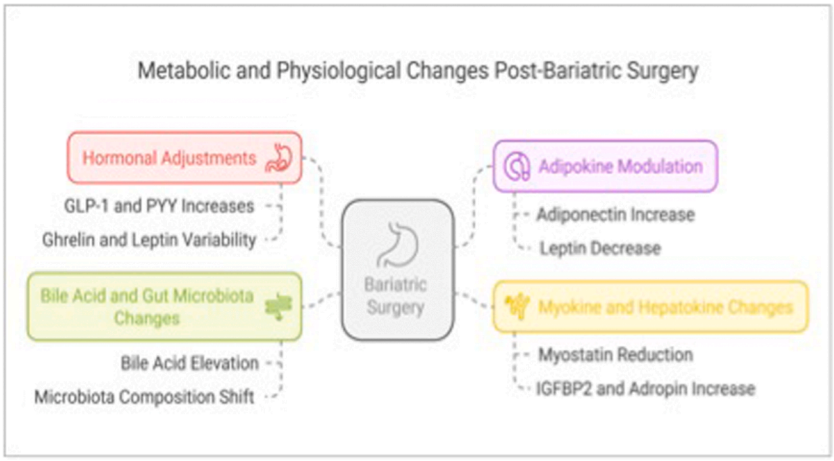

Fig. 2. Metabolic changes postbariatric surgery. IGFBP2 = insulin-like growth factor-binding protein 2; PYY = peptide YY; GLP-1 = glucagon-like peptide-1.

polypeptide (GIP), which improves insulin secretion and glucose control [31,32,33–35,36]. Several studies have provided evidence supporting the role of the Foregut-Hindgut hypothesis in metabolic surgery outcomes. Bariatric procedures such as the duodenal-jejunal bypass (DJB) and ileal interposition have shown significant remission rates of T2DM, suggesting that these surgeries' mechanisms align with the hypothesis. For instance, the DJB with SG has reported remission rates of 73-93%, indicating a strong metabolic effect beyond mere weight loss [33]. Additionally, the rapid improvement in glucose control observed after surgeries like RYGB and BPD, even before significant weight loss, supports the hypothesis that changes in gut hormone secretion play a crucial role [34,37]. However we do have to take into account that procedures like the DJB and ileal interposition are not officially recognized by official societies and some even state that these procedures are still "experimental," despite the growing body of evidence the last decade.

Despite the supporting evidence, the Foregut-Hindgut hypothesis has faced criticism and alternative explanations. Some researchers argue that the hypothesis does not fully account for the metabolic changes observed, as similar diabetes remission rates have been reported in procedures that do not involve foregut exclusion, such as SG with jejuno-jejunal bypass [38]. Moreover, the hypothesis may overlook the role of caloric restriction and changes in bile acid metabolism, which are also significant factors in metabolic improvements postsurgery [35,39]. Additionally, the gastric center hypothesis suggests that changes in the stomach itself, possibly involving unknown hormones, could be responsible for the metabolic benefits observed after MBS [39].

Ileal brake

The "ileal brake" is a physiological feedback mechanism that slows down the transit of food through the gastrointestinal tract to optimize nutrient digestion and absorption. This process is primarily mediated by neurohormonal factors, including gut hormones such as PYY and GLP-1, which are released in response to the presence of undigested nutrients in the ileum [40,41,42]. The mechanism involves a combination of neural and hormonal signals that inhibit gastric emptying and small bowel transit, thereby enhancing nutrient absorption and promoting satiety [40,41]. Post-bariatric surgery, the ileal brake plays a significant role in metabolic and physiological changes. Procedures like BPD/DS and ileal interposition are designed to enhance the activation of the ileal brake by increasing nutrient exposure to the ileum, which can lead to sustained weight loss and improved glycemic control [43,41,44,42]. Compared to other bariatric procedures, these surgeries may offer better long-term outcomes in terms of weight maintenance and resolution of comorbidities such as T2DM [44]. A cohort study by Çelik et al. conducted between 2011 and 2014 evaluated the efficacy of diverted SG with ileal transposition (DSIT) on weight loss and glycemic control in patients T2DM across a spectrum of BMI categories. A total of 131 patients underwent the procedure, with follow-up assessments conducted 1 year postoperatively. The results demonstrated a significant reduction in mean BMI from 33.1 to 23.5 kg/m^2, with weight loss correlating strongly with baseline body weight. However, improvements in glycemic markers including fasting plasma glucose, HbA1C, and insulin sensitivity indices (HOMA-IR and Matsuda Index)—occurred independently of weight loss. Additionally, insulin secretion increased fourfold after surgery despite enhanced insulin sensitivity. These findings suggest DSIT significantly improves glycemic control and insulin sensitivity in T2DM patients, independent of baseline BMI and the degree of weight loss, highlighting its role as an effective metabolic procedure beyond obesity management [45].

Another study by Santoro et al. (2012) presented 5-year outcomes of SG with transit bipartition (SGnull+nullTB) as a metabolic surgical approach for obesity. Conducted on 1020 patients with a BMI range of 33 to 72 kg/m^2, the study introduced TB as a physiologically oriented modification designed to correct gut hormone imbalances associated with high-glycemic diets. The procedure preserves nutrient flow through both the duodenum and ileum, avoiding excluded segments, prostheses, or blind loops, and minimizing malabsorption. Results showed sustained weight loss with an average excess BMI loss of 74% at 5 years and significant metabolic improvements, including 86% diabetes remission. The technique also demonstrated low complication rates (6%) and rare malabsorptive issues. The study concludes that SGnull+nullTB achieve durable weight loss and high diabetes remission without inducing malabsorption, offering a physiologically balanced alternative for MBS [46].

The 2019 HIPER-1 study aimed to compare the metabolic outcomes of four bariatric procedures—OAGB, SG, ileal transposition, and TB with those of medical management in individuals with T2DM. Using mixed-meal tolerance tests conducted 6 to 24 months post-intervention, the study assessed gut hormone secretion, β-cell function, and glycemic control. Results showed that OAGB and ileal transposition were associated with a greater early postprandial rise in plasma glucose levels compared to TB and SG, likely due to pyloric removal and accelerated gastric emptying. Despite elevated GLP-1 levels in the ileal transposition and OAGB groups, β-cell responsiveness to glucose was significantly higher in participants who underwent TB and SG. Notably, postoperative β-cell function emerged as the strongest predictor of hyperglycemia resolution, revealing a disconnect between GLP-1 elevation and β-cell efficacy. These findings suggest that β-cell function, not GLP-1 levels, is the most reliable predictor of glycemic improvement post-surgery, with TB and SG offering superior outcomes in this regard [47].

However despite such promising results across various studies, complications such as delayed gastric emptying and nutrient malabsorption can occur, highlighting the need for careful patient selection and postoperative management [48]. Evidence supporting the ileal brake's role in MBS outcomes includes studies demonstrating significant weight loss and resolution of comorbidities following procedures that enhance ileal nutrient exposure. For example, laparoscopic intestinal bipartition and ileal interposition have shown promising results in terms of weight loss and improvement in T2DM and other obesity-related conditions [40,41,42]. These outcomes are attributed to the sustained activation of the ileal brake, which promotes long-term satiety and reduced caloric intake [42]. While the ileal brake is a compelling mechanism for achieving weight loss and metabolic improvements, some critiques highlight the variability in patient responses and the potential for adverse effects such as nutrient malabsorption and gastrointestinal complications [48]. Alternative viewpoints suggest that a multifactorial approach, considering both surgical and non-surgical interventions, may be necessary to optimize outcomes for patients undergoing MBS [43,44]. Further research is needed to fully understand the long-term implications of ileal brake activation and to refine surgical techniques for better patient outcomes.

Gastric center hypothesis

The gastric center hypothesis suggests that the stomach plays a central role in regulating metabolic processes through the secretion of specific hormones. This hypothesis poses that changes in the stomach, as seen in various MBS, could lead to alterations in hormone secretion, thereby impacting metabolic processes and contributing to weight loss and the remission of metabolic syndrome [49,50]. The hypothesis emphasizes the organ cross talk between the stomach and the brain, suggesting that the stomach may secrete hormones that influence brain activity related to appetite and metabolism. This hormonal and cellular communication is thought to be crucial in regulating appetite and energy balance, potentially explaining the effectiveness of MBS in reducing obesity and its related comorbidities [49,50]. Postsurgery, patients often experience significant metabolic and physiological changes, including weight loss and improved insulin sensitivity. The gastric center hypothesis basically tries to explain the effects of sleeve gastrectomy without a fundamental scientifical basis. The physiological mechanisms of other procedures that involve less alteration in the stomach's anatomy, challenge this hypothesis. Good examples are the the DJB sleeve and ileal transposition surgery [49]. Additionally, the role of gut microbiota and gastrointestinal peptides like ghrelin, gastrin and obestatin in these processes is not fully explained by the gastric center hypothesis [49]. While some studies support the idea that the stomach plays a central role in metabolic regulation, others highlight the lack of evidence for the specific hormones proposed by the Gastric Center Hypothesis. In summary, while the gastric center hypothesis offers an intriguing perspective on the role of the stomach in metabolic regulation, it faces significant challenges due to a lack of empirical evidence and the existence of alternative explanations for the outcomes of MBS [39,49]. Further research is needed to clarify the mechanisms by which these surgeries affect metabolism and to identify the specific roles of gastric hormones and other factors.

Postsurgical metabolic effects on cardiovascular health

Cardiovascular health is significantly impacted by the major hormonal changes brought on by MBS. Hormonal alterations after surgery, such as increases in GLP-1, brain natriuretic peptide (BNP), ghrelin, PYY, and leptin, are

important because they improve metabolic health, reduce inflammation, and improve cardiac function.

A study examined the effects of BNP and GLP-1 on cardiovascular changes after gastric bypass surgery. Patients were assessed based on changes in hormone levels and cardiovascular metrics including heart rate and blood pressure. Following surgery, the results showed a considerable rise in GLP-1 and BNP secretions, which were linked to better cardiovascular outcomes like lower blood pressure and improved heart function. The results point to the possible role of GLP-1 and BNP in promoting postoperative improvements in cardiovascular health by indicating that the cardiovascular advantages of gastric bypass surgery may be partially mediated by increased secretion of these hormones [50]. GLP-1 is also associated with lowering inflammation, enhancing endothelial function, and encouraging vascular regeneration. This implies that the increased GLP-1 levels after MBS may be a target for treatment to treat vascular dysfunction in cardiometabolic-based chronic disease [50,51]. Fig. 3 shows an overview of the cardiovascular effects of GLP-1.

Despite the fact that postoperative ghrelin levels can fluctuate, research on the impact of ghrelin on the heart has produced inconsistent results. Nonetheless, there is evidence that ghrelin increase can enhance a number of cardiac function metrics, such as cardiac index, ejection fraction, and stroke volume index, in addition to lowering left ventricular wall stress in patients with heart failure [52]. Though further research is required to fully understand its processes and therapeutic potential, these findings suggest that ghrelin may contribute to improving cardiac performance, especially in people with impaired heart function [53].

Increased PYY levels were linked to enhanced insulin sensitivity and glycemic management as well as improvements in glucose metabolism. Furthermore, improvements in cardiovascular risk variables, like lower blood pressure and better lipid profiles, were associated with an increase in PYY [54]. Similarly, leptin indicates a possible function in mediating left ventricular hypertrophy (LVH) as it is markedly raised in obese patients and strongly connected with increased left ventricular mass. Left ventricular mass was found to decrease in accordance with a significant fall in leptin levels following MBS and subsequent weight loss. These data indicate that leptin may contribute to cardiac remodeling in obesity and that the reduction in leptin levels post-surgery could play a crucial role in reversing LVH, hence improving cardiovascular health [53,55].

The substantial cardiovascular benefits mediated by these hormonal changes underscore their potential as therapeutic targets for cardiometabolic disorders. With improvements seen in several areas of heart health, MBS has been shown to provide substantial cardiovascular advantages for patients with obesity. The significant decrease in hypertension after surgery is among the most noteworthy outcomes. According to a study, 60–70% of patients experience hypertension remission following the surgery enables a reduction in or discontinuation of antihypertensive medication. Weight loss-induced reductions in sympathetic nervous system

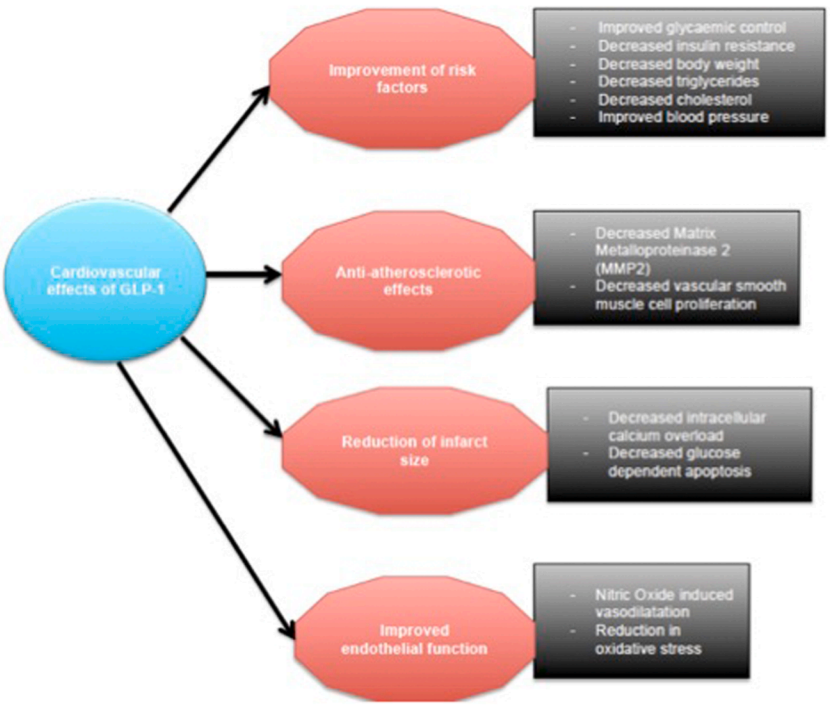

Fig. 3. General overview of the effects of GLP-1 on the cardiovascular system. GLP-1 = glucagon-like peptide-1.

activity and improved endothelial function are primarily responsible for this improvement [56].

MBS not only lowers blood pressure but also improves lipid profiles, which are important for lowering the risk of cardiovascular disease. A study showed that post-operative patients saw a 30–50% drop in triglycerides, a 25–40% decrease in LDL cholesterol, and a 5–15% increase in HDL cholesterol. It is believed that improved lipid metabolism and changed gut hormone production, especially GLP-1, are the causes of these metabolic gains [57].

The advantages also extend to structural enhancements and heart function. Hospitalization rates for heart failure and atrial fibrillation were considerably lower among individuals with pre-existing cardiovascular illness who had MBS [58]. After surgery, a decrease of LVH—a crucial marker of cardiovascular risk—is also observed. According to these results, MBS not only improves pre-existing heart issues but also prevents the heart's function from getting worse [57].

Functionally, several pathways contribute to the reduction of systemic inflammation and to the improvement of vascular health after MBS. According to studies, the surgery was shown to reduce proinflammatory cytokines (such as TNF-α, IL-6) and increase anti-inflammatory adipokines (such as adiponectin), especially in the case of visceral adipose tissue, a relevant contributor to chronic inflammation in obesity [10]. Along with weight loss and metabolic benefits, a long-term decrease in inflammatory markers (CRP, fibrinogen) and enhancement of vascular endothelial status after 2 years postsurgery were shown [59].

Moreover, MBS can reduce obesity-induced systemic inflammation as well as local adipose tissue inflammation that may be mediated by inhibition of macrophage infiltration and restoration of adipocyte function. Since better endothelial function and less oxidative stress increase vascular compliance, these anti-inflammatory benefits help to lower arterial stiffness [57,60].

Gut-brain axis postbariatric surgery

Major alterations in the gut-brain axis are brought about by MBS, which affects eating behavior, neurohormonal signaling, and cognitive function through intricate processes. Changes in gut hormones following MBS, such as GLP-1, PYY, and ghrelin, alter brain pathways that control energy homeostasis, metabolism, and appetite. Reduced appetite and increased fullness are 2 benefits of these hormonal changes, which are mediated by vagal nerve signaling and have direct effects on the brainstem and hypothalamus nuclei. Changes in bile acid metabolism also have an impact on the central nervous system, which may improve metabolic control [61].

Changes in inflammation and cognition after MBS are also influenced by the gut-brain axis. Following surgery, changes in the structure of the gut microbiota might lower systemic inflammation, which may enhance cognitive function. Beneficial gut bacteria's synthesis of short-chain fatty acids (SCFAs) affects neuroinflammation and microglial activation, pointing to a connection between brain health and metabolic improvement. Moreover, improved neuroprotection and cognitive function might result from lower levels of pro-inflammatory cytokines [62]. Following MBS, gut-brain connection also affects disordered eating behaviors, which are prevalent in obesity. Alterations in gut-derived peptides, like GLP-1 and PYY, affect the brain's reward systems and minimize the desire for foods rich in calories. A vital pathway for these signals is the vagus nerve, which sends information from the gut to parts of the brain like the prefrontal cortex and nucleus accumbens that are involved in food motivation. The long-term decline in binge eating and emotional eating behaviors seen in post-surgical patients may be explained by these adjustments [63].

Finally, the effects of MBS on the gut-brain axis are mediated in large part by the gut flora. There has been a noticeable increase in the diversity of microorganisms, including beneficial species like Faecalibacterium prausnitzii and Akkermansia muciniphila. These microorganisms improve the integrity of the intestinal barrier, lower endotoxemia, and generate neuroactive metabolites that affect mood and cognition, such as serotonin and gamma-aminobutyric acid (GABA). The relevance of microbial changes in maintaining metabolic and neurological benefits after MBS is highlighted by the two-way communication between the gut microbiota and the central nervous system. In conclusion, MBS alters the gut-brain axis via microbial, hormonal, and neurological processes, improving metabolic control, lowering inflammation, and changing behavior [64,65].

Challenges and future directions

The postoperative phase of MBS is critical, as patients face several challenges that require careful management to ensure successful outcomes. In the short term, patients may experience gastrointestinal leakage (either leakage of the staple line or anastomosis depending on the type of operation), thromboembolism and infections [66,67]. The complex nature of the procedure and the patient's pre-existing medical conditions may cause these issues. To identify and treat these conditions as soon as possible, close observation is necessary both in the hospital and throughout the early stages of recovery [68,69]. One of the most significant long-term challenges is the risk of nutritional deficiencies. Malabsorption of critical vitamins and minerals, such as iron, calcium, vitamin B12, and folate is quite prevalent. In the absence of appropriate supplementation and consistent monitoring, patients may experience neurological problems, osteoporosis, or anemia [70,71]. Following surgery, patients are needed to follow strict dietary recommendations, which include avoiding high-fat or sugary meals, eating small portions, and following a high-protein diet.

Weight gain or insufficient weight loss may result from noncompliance. Patients also need to make regular physical activity a part of their routines, which can be difficult for people who already struggle with mobility or psychological difficulties [72–75].

According to a systematic review, around 17.6% of patients who undergo MBS experience recurrent weight gain (RWG), with at least 10% of their lost weight returning. Anatomical characteristics such as greater gastric capacity or expanded gastrojejunal stoma diameter, dietary practices like emotional eating and excessive sugar intake, and mental health conditions like anxiety and depression are all associated with RWG. Longer recovery periods and genetic variables also have a role. Reducing RWG and improving long-term results can be achieved by addressing these reasons with customized interventions [76]. To advance our understanding of MBS outcomes, newer experimental setups are needed to substantiate current theories, particularly the gastric center hypothesis, which remains one of the weakest and least understood aspects of MBS mechanisms [77]. Personalized medicine and nutrition are becoming novel strategies to improve the results of MBS. Medical professionals can determine the elements that affect weight loss and comorbidity resolution for each patient by utilizing psychosocial and genetic risk assessments. For instance, customized interventions that target particular requirements are made possible by knowledge of a patient's genetic predispositions, emotional eating behaviors, and metabolic reactions [78–80]. This is furthered by precision nutrition, which tailors meal plans according to lifestyle, metabolic, and genetic variables, maximizing nutritional absorption and promoting long-term weight control after surgery.

Additionally, individuals who don't respond well to conventional methods can benefit from novel solutions provided by developments in personalized devices and therapies, such as pharmacogenomic medicines or adjustable implants [81–83]. By offering patient-specific, tailored care, these technologies hope to improve weight reduction results and lower the risk of difficulties. By addressing these challenges through personalized nutrition, medicine, and tailored interventions, MBS outcomes can be significantly improved, ensuring sustained weight loss, reduced complications, and enhanced quality of life for patients.

Conclusion

MBS is a powerful tool in the management of obesity and related diseases. The insights into its mechanisms, particularly through the lens of hormonal, gut-brain axis, and microbiota changes, have profound implications for both clinical practice and future research. As we continue to explore the intricate interactions that underlie these effects, there is immense potential to refine surgical techniques, personalize treatment approaches, and optimize long-term outcomes for patients, ultimately advancing the field of metabolic surgery and patient satisfaction.

Author contributions

Initial idea: SP. Literature search: SK, AZ. Writing the article: SK, AZ, SP, AC, SU and CP. Final approval: SK, AZ, SP, AC, SU and CP.

Supplementary data

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2025.10.017.

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