The evolving role of metabolic and bariatric surgery in contemporary clinical practice

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Abstract

Metabolic and bariatric surgery (MBS) has long been considered the most effective long-term treatment for severe obesity and its associated comorbidities, including type-2 diabetes mellitus, metabolic syndrome, obstructive sleep apnea syndrome, and cardiovascular disease. Beyond weight loss, MBS has been associated with improved glycemic and metabolic control, lower apnea burden, reduced risk of major adverse cardiovascular events, and improved overall survival. In the last few years, the use of safe and effective weight-loss medications has revolutionized the management of patients with obesity, and may in the future influence referral patterns for MBS. Future research is therefore warranted to clarify the integration between MBS and these novel pharmacological opportunities, with the aim of optimizing patient selection and therapeutic pathways. The aim of this narrative review is therefore to describe the role of MBS in contemporary clinical practice, considering the evolving landscape of pharmacological approaches to treat patients with obesity.

Key words: obesity, metabolic and bariatric surgery, incretin, GLP-1 receptor agonist, tirzepatide

Introduction

The prevalence of obesity and metabolic syndrome has risen dramatically over recent decades, posing a critical global health challenge[1]. According to the World Health Organization, obesity is defined as an abnormal or excessive accumulation of body fat that presents a risk to health, commonly assessed using the body mass index (BMI), where a BMI ≥30 kg/m² classifies an individual as obese.[1] Although BMI does not differentiate between fat and lean mass, nor account for fat distribution, which is a crucial determinant of metabolic risk,[2] it remains the most widely used tool in both clinical and epidemiological settings. Obesity severity is stratified into class I (BMI 30.0–34.9 kg/m²), class II (BMI 35.0–39.9 kg/m²), and class III or severe obesity (BMI ≥40 kg/m²).[2] Global obesity rates have nearly tripled since 1975, with over 650 million adults classified as affected by obesity in 2022,[3] creating an urgent need for effective interventions to mitigate its health, economic, and social burden.

Obesity is independently associated with poor quality of life, increased risk of incident cardiovascular disease (CVD), and all-cause mortality.[4,1] Furthermore, it represents the substrate of metabolic syndrome (including dyslipidemia, hypertension, and insulin resistance), type-2 diabetes mellitus (T2DM), and obstructive sleep apnea syndrome (OSAS), which synergistically increase cardiovascular risk and worse outcome.[1] Lifestyle modification through dietary changes, physical activity, and behavioral therapy remains the first-line approach,[1] but often fails in achieving sustainable weight loss, particularly in case

of severe obesity. While safety concerns have limited to use of pharmacological approaches to treat obesity in the past,[5] glucagon-like peptide-1 receptor agonists (GLP-1RA) and tirzepatide (a dual glucose-dependent insulinotropic polypeptide [GIP] and GLP-1RA) have demonstrated meaningful weight loss and metabolic improvements without major safety concerns.[5]

Metabolic and bariatric surgery (MBS) has long been considered the most effective intervention for achieving substantial and durable weight loss in patients with severe obesity and/or refractory metabolic syndrome.[6] Indeed, the long-term benefits of MBS include improvement or remission of T2DM, hypertension, and OSAS, as well as reductions in cardiovascular risk and mortality.[7,8] These effects are mediated by a combination of mechanical, hormonal, and metabolic mechanisms, some of which overlap with emerging pharmacological treatments.[9] However, MBS is not without limitations. Short-term risks include perioperative complications, nutritional deficiencies, and the need for reoperation in a minority of patients.[10] Long-term challenges include weight regain, the requirement for lifelong micronutrient supplementation, variable access to surgery across healthcare systems, and limited uptake in eligible patients due to factors such as referral patterns, patient preferences, and insurance coverage.[10] Furthermore, the rapid development of effective pharmacotherapy raises questions about the evolving role of MBS in the treatment algorithm for patients with obesity, particularly in less severe cases or in populations where medications may yield comparable outcomes.

Therefore, the aim of this narrative review is to summarize the current evidence and clinical role of MBS in the modern therapeutic landscape, focusing on its indications,

mechanisms, benefits, and limitations, and discuss how surgery may integrate with novel pharmacological approaches.

Methodology

A comprehensive search of the PubMed database (and supplemented with relevant references from Medline, Embase, Scopus, and Google Scholar) was performed on December 15, 2024, to retrieve peer-reviewed, English-language studies involving human subjects investigating the role of MBS and novel weight-loss medications published in the last 15 years. The following MeSH terms were considered for the search: obesity, BMI, weight loss, metabolic surgery, bariatric surgery, sleeve gastrectomy, gastric bypass, anti-obesity drugs, GLP-1 receptor agonists, semaglutide, liraglutide, dual and triple agonists, tirzepatide. In cases of overlapping content, the most relevant and rigorous evidence was prioritized, favoring international over national guidelines, systematic review and meta-analysis over single studies, randomized trials over observational studies, controlled over uncontrolled designs, propensity score–matched analyses when available, and more recent publications over older ones. As a narrative review, the findings should be interpreted as a qualitative synthesis rather than a systematic evaluation of all available evidence.

Indications and contraindications to metabolic and bariatric surgery

It is widely accepted that a multidisciplinary team is essential for the safe and effective delivery of MBS services. According to the updated American Society for Metabolic and Bariatric Surgery/International Federation for the Surgery of Obesity and Metabolic Disorders (ASMBS/IFSO) 2022 guidelines,[8] the decision to refer a patient for surgery should be made following a comprehensive interdisciplinary assessment.[8] The core team typically includes a physician (usually an endocrinologist), bariatric surgeon, anesthesiologist, psychologist or psychiatrist, dietitian, and a nurse practitioner.

The indications to MBS have evolved significantly over time. The 2022 ASMBS/IFSO guidelines[8] were developed to replace the outdated 1991 NIH Consensus Statement on Bariatric Surgery.[11] According to the updated ASMBS/IFSO 2022 guidelines, indications for MBS have significantly expanded, reflecting clinical and metabolic benefit across broader BMI ranges and patient categories. A visual summary of guideline-based indications and special populations is provided in **Figure 1**, to which the reader is referred for detailed thresholds and recommendations.

Beyond weight loss and metabolic control, MBS can serve as a bridge to other surgical interventions or treatments in selected patients. In patients with BMI ≥30 kg/m^2 who are candidates for joint arthroplasty, MBS may reduce operative time, hospital length of stay, and postoperative complications.[12] In individuals with abdominal wall hernias, performing MBS prior to hernia repair may significantly reduce postoperative complication rates and recurrence.[13] While MBS should be avoided in patients with decompensated cirrhosis, it has been associated with histologic improvement of nonalcoholic steatohepatitis and regression of fibrosis in early cases, leading to a reduced risk of hepatocellular

carcinoma.[14,15] MBS may be considered in individuals on cardiac and renal transplant waiting lists. In this respect, in patients with heart failure (HF), MBS has been associated with improvements in left ventricular ejection fraction, functional capacity, and increased likelihood of successful transplantation.[8]

According to guidelines,[8] psychiatric disorders such as schizophrenia or bipolar disorder are not absolute contraindications to MBS, if well-controlled prior to surgery. On the other hand, absolute contraindications to MBS are: 1) uncontrolled severe psychiatric illness, such as untreated major depression, active psychosis, or poorly managed bipolar disorder, which may impair the patient's ability to comply with postoperative care; 2) uncontrolled eating disorders, including bulimia nervosa and binge eating disorder, which may interfere with surgical success and potentially worsen postoperatively; 3) active substance abuse, including ongoing alcohol or drug misuse, due to the heightened risk of perioperative complications; 4) cognitive or behavioral inability to understand or comply, i.e., patients who lack the capacity to comprehend the procedure, its risks, and the necessary lifestyle changes; 5) limited life expectancy, including patients with active or advanced malignancies, uncontrolled end-stage renal disease, or decompensated cardiopulmonary disease, where the risks of surgery are likely to outweigh the potential benefits; 6) severe coagulopathies, which may substantially increase bleeding risk; 7) inability to tolerate general anesthesia.[8]

Overview of metabolic and bariatric surgery procedures

Comparative characteristics of the major MBS procedures, including mechanistic emphasis and relative metabolic impact, are summarized in **Figure 2** for rapid clinical reference. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most commonly performed, accounting for approximately 90% of all interventions worldwide.[8] SG involves removing 80–85% of the stomach to create a narrow sleeve, thus reducing food intake and hunger.[7] On the other hand, RYGB combines restrictive and malabsorptive components by creating a small gastric pouch and rerouting the small intestine to bypass much of the stomach and duodenum.

Other options include the one-anastomosis gastric bypass (OAGB) and single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S).[8,16] OAGB features a simpler design than RYGB, involving a single connection between the gastric pouch and small intestine, while SADI-S combines a SG with a single intestinal anastomosis, leading to malabsorption and hormonal changes.[8,16] The biliopancreatic diversion (BPD) and its variation – i.e., the duodenal switch – are highly effective but complex procedures that combine SG with an extensive intestinal bypass, leading to significant weight loss and metabolic improvement at the cost of higher risks of nutritional deficiencies.[16]

Less invasive approaches for MBS have been developed to reduce the surgical risk.[17,18] Among these, endoscopic SG holds promise but requires further evidence, while endoscopic duodenal-jejunal bypass, not altering stomach capacity, is aimed at targeting glucose metabolism rather than weight loss.[17,18]

The choice among these procedures should be tailored according to both and individual patient factors, such as obesity severity, comorbidities, and treatment goals.

Molecular mechanisms of metabolic and bariatric surgery

Although multiple biological mechanisms have been proposed to explain the metabolic benefits of MBS, causal attributions remain tentative and are highly dependent on the type of surgical procedure, baseline metabolic profile, and individual host phenotype. Therefore, mechanistic interpretations should be considered hypothesis-generating rather than definitive. A schematic representation of the key proposed hormonal and metabolic pathways involved is presented in **Figure 3**, which integrates mechanisms relevant to both weight-dependent and weight-independent effects.

Rapid nutrient delivery to the distal intestine after surgery enhances postprandial secretion of incretins, including GLP-1, peptide YY, and oxyntomodulin,[19] which promote satiety, reduce appetite, and improve glucose-dependent insulin secretion.[20] Meanwhile, the secretion of the orexigenic hormone ghrelin is reduced, contributing to decreased hunger.[21] These hormonal shifts may occur within days after surgery, often before significant weight loss is achieved.

Additional mechanisms include alterations in bile acid metabolism that influence glucose and lipid homeostasis as well as inflammatory pathways.[20,22] Changes in gut microbiota composition following MBS have been linked to improved gut barrier function, increased short-chain fatty acid production, and enhanced systemic insulin sensitivity.[23]

However, such microbial changes are heterogeneous, depending on procedure type, baseline host factors, and duration of follow-up, and not all studies consistently report increased diversity or uniform taxonomic shifts.[24,25] The effects of MBS on the microbiota therefore appear to be individualized and multifactorial, with their precise clinical significance still under investigation.[24] Furthermore, increases in fibroblast growth factors and epigenetic modifications in genes regulating insulin signaling and energy metabolism have been reported, though their precise clinical relevance remains under investigation.[26–28]

Neurological adaptations also contribute to the long-term success of MBS. By reshaping gut-brain communication, MBS reduces hunger signals (e.g., modulating agouti-related peptide and neuropeptide Y activity) and enhances satiety (e.g., upregulating pro-opiomelanocortin neurons).[22] Interestingly, also changes in brain reward centers have been documented, and may contribute to reduce craving for calorie-dense foods, encouraging healthier eating behaviors.[23]

Clinical benefits of metabolic and bariatric surgery

As anticipated, the clinical benefit of MBS extends beyond weight reduction. Several studies indeed demonstrated the positive effects of MBS on many obesity-related comorbidities, including systemic arterial hypertension, dyslipidemia, T2DM, and OSAS (**Supplementary Table 1**).

Weight loss

Substantial and sustained weight loss is often the primary goal of MBS.[29–31] The extent of weight reduction varies depending on the procedure, with RYGB leading to the greatest mean percentage weight loss (25–35%), followed by SG (20–30%) and OAGB (17–20%).[29,31,32] Maximum weight loss is typically observed within 1–2 years post-surgery, with long-term durability.[29] Notwithstanding, individual responses vary, and higher preoperative BMI, older age, male sex, and preexisting T2DM, particularly in insulin users, have been identified as predictors of a lower weight loss.[33] Moreover, weight regain may affect up to 30% of patients, depending on baseline BMI[34] and type of surgery.[35]

Systemic hypertension and dyslipidemia

Systemic hypertension is significantly ameliorated following MBS. Pooled data from two randomized clinical trials comparing laparoscopic RYGB and SG demonstrated that, after 5 years, 60.3% in the RYGB group and 44.9% in the SG group had discontinued antihypertensive medication, slightly favoring RYGB (p=0.049).[32,36,37] Furthermore, surgery is linked to a 4-fold reduction in hypertension incidence[38] and a 6-fold higher success rate in reducing antihypertensive drug use and achieving blood pressure control compared to medical therapy alone.[39]

Not surprisingly, the benefit of MBS extends to dyslipidemia as well, decreasing triglyceride levels up to 40% and increasing high-density lipoprotein cholesterol up to 20–

30%.[7,38] These changes are driven by weight loss, improved insulin sensitivity, and alterations in gut microbiota and bile acid metabolism.[20]

Type-2 diabetes mellitus

Among the most compelling benefits of MBS is its profound impact on glycemic control.[40,41] This has been extensively documented, and, in a long-term pooled analysis,[42] MBS was associated to a mean HbA1c reduction of 1.5% to 3%, leading to T2DM remission in many patients (up to 60-80% in some studies).[43] The likelihood of T2DM remission depends on the surgical procedure, disease duration, and used remission criteria.[40,44–46] Generally, BPD shows the highest remission rates, followed by RYGB, and SG.[47] Remission is more likely in patients who achieve greater weight loss, have a shorter history of T2DM, and preserved pancreatic function.[48] More granular 5-year data are provided by the Diabetes Surgery Study[46], in which adults with poorly controlled T2DM (baseline HbA1c ~9.6%) and BMI 30.0–39.9 kg/m^2 were randomized to intensive lifestyle–medical management with or without RYGB. At 5 years, 23% of patients in the RYGB group versus 4% in the lifestyle–medical group achieved the composite triple endpoint (HbA1c <7.0%, LDL-C <100 mg/dL, systolic blood pressure [BP] <130 mmHg; absolute difference 19%, 95% confidence interval [CI] 4–34%; p=0.01), and 55% versus 14% achieved HbA1c <7.0% (absolute difference 41%, 95% CI 19–63%; p=0.002)[46]. Mean HbA1c was 7.1% in the RYGB group versus 8.7% in the lifestyle–medical group at 5 years, corresponding to a net treatment difference of −1.6 percentage points (95% CI −2.2 to −1.0; p<0.001). RYGB also allowed substantial de-escalation of

antihyperglycemic therapy, with non-insulin diabetes medications used by 42% versus 88% of patients at 5 years and insulin use in 15% versus 37% of patients in the surgical versus non-surgical group, respectively[46]. Beyond glicemic control, MBS significantly lowers the incidence of microvascular complications such as nephropathy, neuropathy, and retinopathy.[45,49,50] Despite these benefits, some patients may experience T2DM relapse overtime. However, even in this subset, long-term follow-up studies have shown superior glycemic control compared to a non-surgical approach.[45]

Obstructive sleep apnea syndrome

Obesity and OSAS are bidirectionally linked: obesity exacerbates upper airway collapse, triggering OSAS, while OSAS-related sleep fragmentation contributes to weight gain and metabolic dysfunction.[51] In a large matched cohort of 13,657 patients with moderate-to-severe OSAS and BMI 35–70 kg/m^2, MBS was associated with a significantly lower 10-year incidence of major adverse cardiovascular events (MACE, 27.0% vs 35.6%; adjusted hazard ratio [HR] 0.58, 95% CI 0.48–0.71) and all-cause mortality (9.1% vs 12.5%; adjusted HR 0.63, 95% CI 0.45–0.89) compared with nonsurgical care over a median follow-up of 5.3 years.[52] Strikingly, MBS significantly reduced the apnea-hypopnea index, from 38 to 11 events/h, along with improved oxygen desaturation severity.[52]

Cardiovascular events

The principal cardiovascular benefits associated with MBS are summarized in the **Graphical Abstract**. In a large matched-cohort study including 13,722 individuals, MBS was associated with a significantly lower 8-year cumulative incidence of MACE compared with usual care (30.8% vs. 47.7%; adjusted HR 0.61, 95% CI 0.55–0.69)[53]. Importantly, the cardiovascular benefit remained consistent across sex, age, BMI, diabetes duration, and renal function strata. When individual components of the composite outcome were examined, MBS was associated with lower rates of all-cause mortality (10.0% vs. 17.8%; HR 0.59, 95% CI 0.48–0.72), HF (6.8% vs. 18.9%; HR 0.38, 95% CI 0.30–0.49), nephropathy (6.1% vs. 16.3%; HR 0.40, 95% CI 0.31–0.52), coronary artery disease (7.9% vs 11.6%; HR 0.69, 95% CI 0.54–0.87), cerebrovascular disease (4.1% vs 5.6%; HR 0.67, 95% CI 0.48–0.94), and atrial fibrillation (AFib, 7.9% vs 13.6%; HR 0.78, 95% CI 0.62–0.97). Similar protection was observed for the traditional 3-component MACE endpoint of myocardial infarction, ischemic stroke, and death (17.0% vs 27.6%; HR 0.62, 95%CI 0.53–0.72)[53]. These findings align with evidence from a recent meta-analysis of 174,772 individuals, demonstrating a 49.2% reduction in all-cause mortality and a median life expectancy gain of 6.1 years after MBS compared with usual care, with even greater benefit observed in patients with T2DM (median gain 9.3 years vs 5.1 years in individuals without diabetes)[54]. In addition to these epidemiological outcomes, complementary studies suggest approximately 60% lower risk of acute myocardial infarction over 11-year follow-up[55], alongside imaging data indicating attenuated atherosclerotic progression and improved myocardial perfusion[56,57]. While these findings point toward possible cardiovascular advantages of MBS, they are derived from

observational and mechanistic studies and therefore cannot establish causality or confirm a survival benefit.

The benefits of MBS have been described also in patients with HF.[58,59] Limited observational studies have demonstrated meaningful improvements in cardiac function following surgery, including increases in LVEF by approximately 5–10% from baseline and significant improvement in functional capacity (e.g., NYHA class reduction and increased exercise tolerance)[60,61]. Additionally, MBS has been associated with greater access to advanced therapies: in a cohort of 2,798 patients with left ventricular assist device support, prior MBS was associated with a three-fold higher probability of successful heart transplantation during follow-up[62]. These data suggest that MBS may play a valuable role in optimizing candidacy for advanced cardiac therapies and improving clinical status prior to transplantation. The reduction in blood pressure and improved hemodynamics contribute to decreasing left ventricular mass and improving cardiac function.[63,64] Accordingly, Doumouras *et al*. reported a 19.3% absolute risk reduction in HF incidence following MBS.[65]

With regard to AFib, the Swedish Obese Subjects study reported a 29% reduction in new-onset AFib following MBS compared to usual care over a median 19-year follow-up,[66] particularly in younger patients and those with higher baseline diastolic blood pressure. By contrast, other studies have not confirmed a significant protective effect.[59,67] This inconsistency may be explained by heterogeneity in AFib ascertainment (clinical diagnosis vs. systematic screening), baseline risk factor profiles, and follow-up duration. Beyond new-onset AF, emerging data suggest that MBS may also influence procedural outcomes in patients undergoing AF ablation. In a retrospective cohort of morbidly obese patients, pre-

ablation MBS was associated with substantially lower AF recurrence (20% vs. 61%; p<0.0001) and fewer repeat ablation procedures (12% vs. 41%; p<0.0001) compared with non-surgical controls over 36 months of follow-up.[68]

Cost-effectiveness of metabolic bariatric surgery

The cost-effectiveness of MBS is a key consideration in treatment decision-making, particularly in the context of emerging medical therapies for obesity.

While MBS requires significant upfront investment, especially for procedures like laparoscopic RYGB, the short-term costs are offset by early clinical benefits. Among surgical options, RYGB has shown the highest effectiveness, yielding 17.07 quality-adjusted life years (QALYs), compared with 16.56 for SG, 16.10 for laparoscopic adjustable gastric banding (LAGB), and 15.17 for medical management.[69] In particular, SG was identified as the most cost-effective option for individuals with a BMI of 35.0–39.9 kg/m^2, whereas RYGB was more favorable for those with BMI ≥40 kg/m^2.

Multiple analyses have demonstrated that MBS is cost-saving also in the long term due to reductions in medication use, fewer hospital admissions, and improved management of obesity-related comorbidities. A cost-utility analysis in England estimated average savings of € 2,742 per patient following surgery.[70] Similarly, a large cohort study funded by the UK National Institute of Health Research found an incremental QALY gain of 2.142, with a cost per QALY of £ 7,129.[71] In Spain, bariatric surgery was associated with 4.4 additional QALYs

compared to conservative management over a patient's lifetime. Over a 10-year horizon, the cost per QALY was € 5,966, which is well below commonly accepted thresholds for cost-effectiveness.[72]

Surgery has also proven to be particularly cost-effective in patients with T2DM. Ackroyd et al. reported superior cost-effectiveness of RYGB and AGB compared to medical therapy for T2DM.[73] The Swedish Obese Subjects study further confirmed that long-term healthcare costs were significantly reduced in surgically treated patients, especially among those with baseline hyperglycemia.[74] It should be noted that most of the available evidence in this context predates the clinical availability of newer pharmacotherapies, whose long-term cost-effectiveness remains under evaluation. These medications incur ongoing expenses and may require lifelong administration, unlike surgery, which offers a potential one-time intervention with durable results.

Challenges and controversies of metabolic and bariatric surgery

Despite its well-documented benefits, MBS remains underutilized worldwide, with only 1% to 2% of eligible patients being referred to MBS each year.[75]

Several reasons may contribute to this discrepancy. At the healthcare system level, inconsistent insurance coverage and high out-of-pocket costs are major deterrents, particularly in countries where MBS is not universally reimbursed.[75] Indeed, although the procedure is cost-effective in the long term, the initial financial burden remains prohibitive for many patients. Further systemic barriers such as long waiting lists, limited surgical

capacity, and uneven geographical distribution of specialized centers restrict access, especially in resource-limited settings.[75]

Another critical concern regards preoperative risk assessment, often enhanced by the burden of comorbidities in many candidates. Different surgical techniques have varying risks and benefits depending on the patient's metabolic profile and comorbidities.[76] For example, RYGB carries a higher risk of early complications and readmissions, especially when compared to SG.[76] Therefore, in absence of definitive evidence about the superiority of any technique, a personalized approach, based on both local expertise and patient features remains warranted. Advances in minimally invasive techniques, including robotic-assisted procedures, aim to improve surgical precision, reduce complications, and shorten recovery times. Additionally, endoscopic metabolic interventions, such as endoluminal SG, may offer an alternative for patients who are not candidates for traditional surgery.

Intraoperative and postoperative complications also pose significant challenges. Intraoperatively, surgeons must manage technical difficulties related to previous abdominal surgeries, excessive visceral fat, and anesthesia-related risks. The most common early postoperative complications include gastrointestinal bleeding, anastomotic leaks, and fistula formation, as well as surgical site infections and deep vein thrombosis.[36,37] Furthermore, nausea and vomiting can delay recovery and impact nutritional status. Long-term complications include anemia, gastroplegia, marginal ulcers, and esophagitis.[40,45]

In this respect, a close, well-structured, patient follow-up of operated patients is mandatory, also to prevent the most common causes of mortality, which are pulmonary

embolism, pneumonia, and anastomotic leakages.[40] Multidisciplinary management is the key to long-term success.[8] In addition to addressing nutritional deficiencies – particularly in iron, vitamin B12, calcium, and fat-soluble vitamins – comprehensive care should also encompass structured lifestyle modification both pre- and post MBS.[8] Evidence demonstrates that structured nutritional counseling, individualized physical activity plans, and psychological and behavioral support programs contribute significantly to optimizing surgical outcomes, reducing the risk of postoperative complications, and improving long-term weight stabilization and quality of life[46,77,78]. Participation in supervised behavioral interventions has been associated with reduced weight regain and greater adherence to nutritional and supplementation protocols[79]. The incorporation of these multidisciplinary strategies is strongly recommended in current ASMBS/IFSO guidelines, highlighting their role as integral to the success of MBS rather than adjunctive or optional components.

The long-term management of psychiatric conditions is also crucial, given the high prevalence of pre-existing mental health disorders among patients with obesity.[8] In this respect, a meta-analysis of over 148,000 of patients undergoing MBS reported a nearly 2-fold increase in self-harm/suicide attempts after surgery compared to preoperative rates and 3-fold higher risk compared to BMI- and age-matched controls.[80] While some studies suggest that RYGB may be associated with a higher risk compared to purely restrictive procedures,[80] these findings should be interpreted with caution. The underlying mechanisms are likely multifactorial, involving psychiatric vulnerability, altered pharmacokinetics of alcohol and psychotropic medications after malabsorptive procedures, and psychosocial factors such as body image distress or weight regain. Given these

uncertainties, robust prospective data are still needed, and comprehensive long-term psychological support should be considered an essential component of MBS follow-up care.

Further steps are necessary to optimize patient referral to MBS. Indeed, current criteria are still largely based on BMI thresholds.[8] While BMI is simple to measure and useful for population screening, it is an imperfect predictor of long-term outcomes after surgery, not accounting for differences in body composition, fat distribution, metabolic profile, or comorbidity burden.[81] More nuanced assessment tools, such as the Edmonton Obesity Staging System (EOSS), have been proposed to improve patient selection. EOSS integrates clinical, functional, and psychological parameters to classify patients into stages 0–4, with higher stages associated with progressively greater morbidity and mortality risk, independently of BMI.[82] Incorporating EOSS, or similar multidimensional scores, into future guidelines could help prioritize patients most likely to derive clinical benefit from MBS, while avoiding unnecessary procedures in those at lower risk.

Metabolic and bariatric surgery in the era of novel pharmacological therapies

The introduction of highly effective weight-loss pharmacotherapies, including GLP-1 receptor agonists and dual GIP/GLP-1 agonists, has significantly reshaped the therapeutic landscape of obesity and raised important questions regarding their optimal positioning relative to MBS[5,83]. Modern agents such as semaglutide and tirzepatide can achieve 15–22% total weight loss in clinical trials[84], whereas retatrutide ("triple agonist") has demonstrated

up to 24% total weight loss in phase-2 data[83,85]. In comparison, MBS continues to provide the greatest expected magnitude of weight reduction, with RYGB typically achieving 25–35% total weight loss and SG 20–30%, together with well-documented durability over 10–20 years. Beyond weight loss, the benefits of these drugs extends to glycemic control, with patients on tirzepatide being >16-fold more likely to reach T2DM in clinical trials, and other obesity-related comorbidities, such as HF with preserved ejection fraction,[86] OSAS,[87] and metabolic dysfunction-associated steatohepatitis.[88]

Two recent comparative observational studies provide the first head-to-head evidence between these modalities. In a large matched-cohort analysis including 6,070 patients with obesity and T2DM, MBS was associated with a 62% reduction in mortality compared with GLP-1RA therapy among individuals with a diabetes duration ≤10 years, mediated by greater weight loss, whereas no difference in mortality was observed in those with longer diabetes duration[89]. Importantly, rates of MACE were comparable between groups[89]. More recently, a United States claims-based analysis including 30,458 patients with class II–III obesity demonstrated that MBS was associated with significantly greater weight loss compared with GLP-1RA therapy (28.3% vs 10.3%; $p<0.001$) and with lower 2-year cumulative costs ($51,794 vs. $63,483; $p<0.001$) due to persistently high pharmacotherapy expenses[90].

However, evidence from randomized controlled studies directly comparing MBS and pharmacotherapy is still expected. Unlike MBS, which is supported by extensive long-term data demonstrating durable metabolic benefit and survival advantage, real-world long-term evidence for pharmacotherapy remains limited, and observational cohorts document significant treatment discontinuation rates over time. These considerations are essential in

guiding patient selection and long-term management strategies and reinforce the importance of individualized therapeutic sequencing rather than binary treatment comparisons.

Current data suggest that MBS may retain therapeutic priority in patients in whom durable and maximal weight loss is the primary objective - particularly among younger individuals with shorter diabetes duration and substantial metabolic burden - whereas pharmacotherapy may be more appropriate as initial therapy in individuals with less severe obesity, in settings where surgery is contraindicated or undesired, or where accessibility and cost constraints favour a non-procedural approach. Furthermore, integration of the two modalities is likely to become increasingly relevant. Pre-operative GLP-1RA treatment may improve metabolic risk profiles and facilitate surgical safety in high-risk patients[91], while postoperative use has shown benefit in mitigating insufficient weight loss or weight regain.

Taken together, treatment strategy should be guided by patient phenotype, therapeutic role within the longitudinal care pathway, and the feasibility of sustaining long-term benefit. Rather than positioning MBS and pharmacotherapy as competing alternatives, an integrated approach recognizes the complementary potential of each modality depending on clinical context. Accordingly, **Figure 4** presents a simplified algorithm illustrating potential decision-making pathways based on: (i) clinical phenotype and risk profile, (ii) therapeutic timing within the care pathway (first-line therapy, pre-operative optimization, or post-operative treatment of insufficient weight loss/weight regain), and (iii) long-term feasibility and durability considerations.

Defining optimal sequencing strategies and identifying patient subgroups most likely to benefit from pharmacotherapy versus surgery - or from combined approaches - represents a key priority for future prospective research.

Study limitations

As a narrative review, this study does not include formal dual-reviewer screening, structured risk-of-bias assessment, predefined grading of evidence, or quantitative meta-analytic synthesis. These methodological characteristics may introduce selection bias and limit the comparability of included studies. Therefore, the findings should be interpreted as a qualitative synthesis rather than a systematic evaluation of all available evidence. Moreover, several limitations should be acknowledged. Evidence guiding patient selection remains largely derived from observational cohorts and continues to rely predominantly on BMI thresholds rather than multidimensional stratification systems. Similarly, mechanistic studies vary substantially in methodology, duration, and endpoints, limiting the ability to draw definitive conclusions about causal pathways. While long-term outcome data consistently demonstrate reductions in mortality and cardiovascular risk, they predominantly originate from large cohort registries rather than randomized clinical trials. Economic analyses are further constrained by differences across healthcare systems and may not yet fully reflect the evolving landscape shaped by novel anti-obesity pharmacotherapies. Finally, evidence regarding the optimal integration of pharmacotherapy with surgical approaches remains preliminary, with a need for well-designed prospective

and comparative studies. These considerations highlight the importance of cautious interpretation and underscore the need for future research to clarify unresolved questions across these domains.

Conclusions and future perspectives

Obesity has reached pandemic proportions, significantly contributing to chronic illnesses such as T2DM and CVD. Despite advances in lifestyle interventions and pharmacologic treatments, MBS remains an effective and durable strategy for achieving substantial and sustained weight loss, as well as potential remission of obesity-related comorbidities.

Nonetheless, the future of MBS lies in continuous innovation, particularly through integration with emerging weight-loss therapies. Such a pharmacological revolution has two major implications for MBS. First, the significant weight loss achieved with these agents raises the possibility that, in the future, the profile of patients referred to surgery may change. However, the long-term effect of these therapies on surgical eligibility and outcomes remains to be determined. Second, for patients requiring surgical intervention, preoperative pharmacological treatments could improve metabolic status, reduce surgical risks, facilitate intraoperative management, and enhance postoperative outcomes. This is particularly relevant for individuals with severe obesity, T2DM, or cardiovascular comorbidities, where even a modest preoperative weight reduction may lower operative risk. Despite the promising potential of these new therapies, several uncertainties remain

regarding their long-term effectiveness, adherence, and cost-effectiveness compared to MBS.

Given the complexity and heterogeneity of obesity as a disease, an integrated and complementary rather than competitive relationship between MBS and pharmacologic therapies will likely be the most effective strategy for long-term management. Future research should aim to identify patient subgroups who may benefit most from pharmacological therapy alone versus those requiring surgery, and to determine whether a combined approach yields superior long-term metabolic outcomes.

Figure Legends

Figure 1. 2022 ASMBS/IFSO indications for metabolic and bariatric surgery.

Color coding reflects traditional guideline recommendation classes: Class I (*green*), Class II (*yellow*).

ASMBS, American Society of Metabolic and Bariatric Surgery; BMI, body mass index; IFSO, International Federation for the Surgery of Obesity and Metabolic Disorders; T2DM, type 2 diabetes mellitus.

Figure 2. Overview of metabolic and bariatric surgery (MBS) procedures.

Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most commonly performed operations worldwide. Alternative approaches include one-anastomosis gastric bypass (OAGB), single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S), and biliopancreatic diversion/duodenal switch (BPD/DS), which vary in complexity, efficacy, and nutritional risks. Endoscopic options, such as endoscopic SG and duodenal-jejunal bypass, represent less invasive investigational strategies. Choice of procedure should be individualized according to obesity severity, comorbidities, and treatment goals.

Figure 3. Molecular mechanisms of MBS.

The benefits of metabolic and bariatric surgery are due to both anatomical and malabsorptive effects (gastric restriction, intestinal bypass) and metabolic and endocrine adaptations (gut–brain axis changes, improved insulin sensitivity, altered bile acid signaling, gut hormone dynamics, and microbiota modifications). AgRP, agouti-related peptide; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; NPY, neuropeptide Y; OXM, oxyntomodulin; POMC, pro-opiomelanocortin; PYY, peptide YY; TGR5, Takeda G-protein receptor 5.

Figure 4. Proposed clinical decision-making algorithm for integrating MBS and pharmacotherapy in obesity management.

This algorithm illustrates potential treatment pathways based on patient phenotype, therapeutic timing within the longitudinal care continuum, and feasibility of sustaining long-term benefit. Pharmacotherapy may be used as first-line therapy in individuals with less severe obesity or when surgery is contraindicated or undesired, as pre-operative optimization to improve metabolic risk profiles in high-risk surgical candidates, or as post-operative therapy to address insufficient weight loss or weight regain. MBS remains the most effective option for achieving durable and maximal weight loss, particularly in patients with severe obesity and shorter diabetes duration. The choice between strategies should be individualized, acknowledging differences in efficacy, durability, adherence, and real-world cost and accessibility considerations.

Graphical Abstract. Beneficial effects of metabolic and bariatric surgery on obesity-related cardiovascular risks.

AFib, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricular; MS, metabolic surgery; NO, nitric oxide; OSAS, obstructive sleep apnea syndrome; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; T2DM, type 2 diabetes mellitus.

Author Contributions

GP, FG and ME contributed to the conception or design of the work. GP and FG drafted the manuscript. MN and ME critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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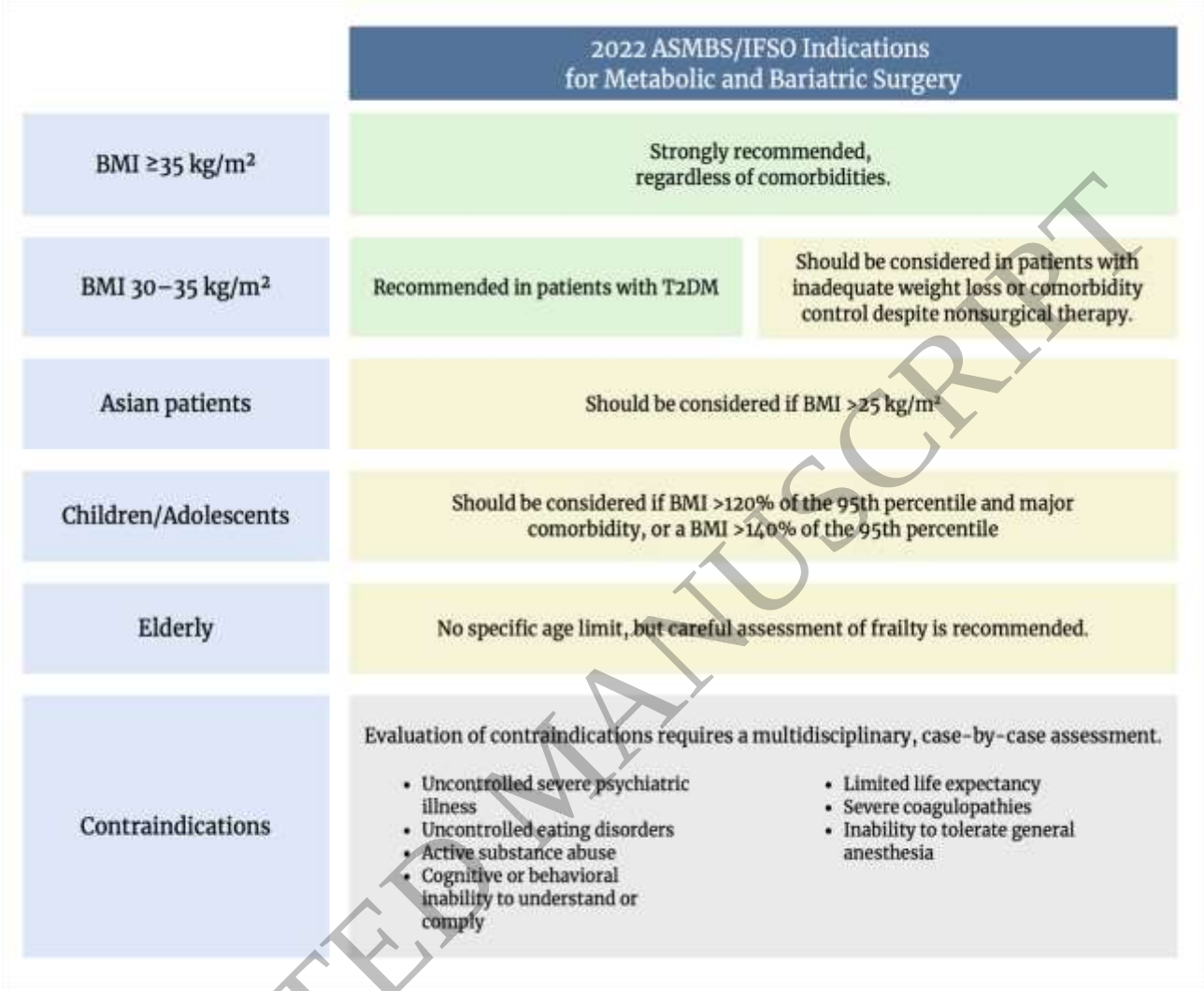

Figure 1
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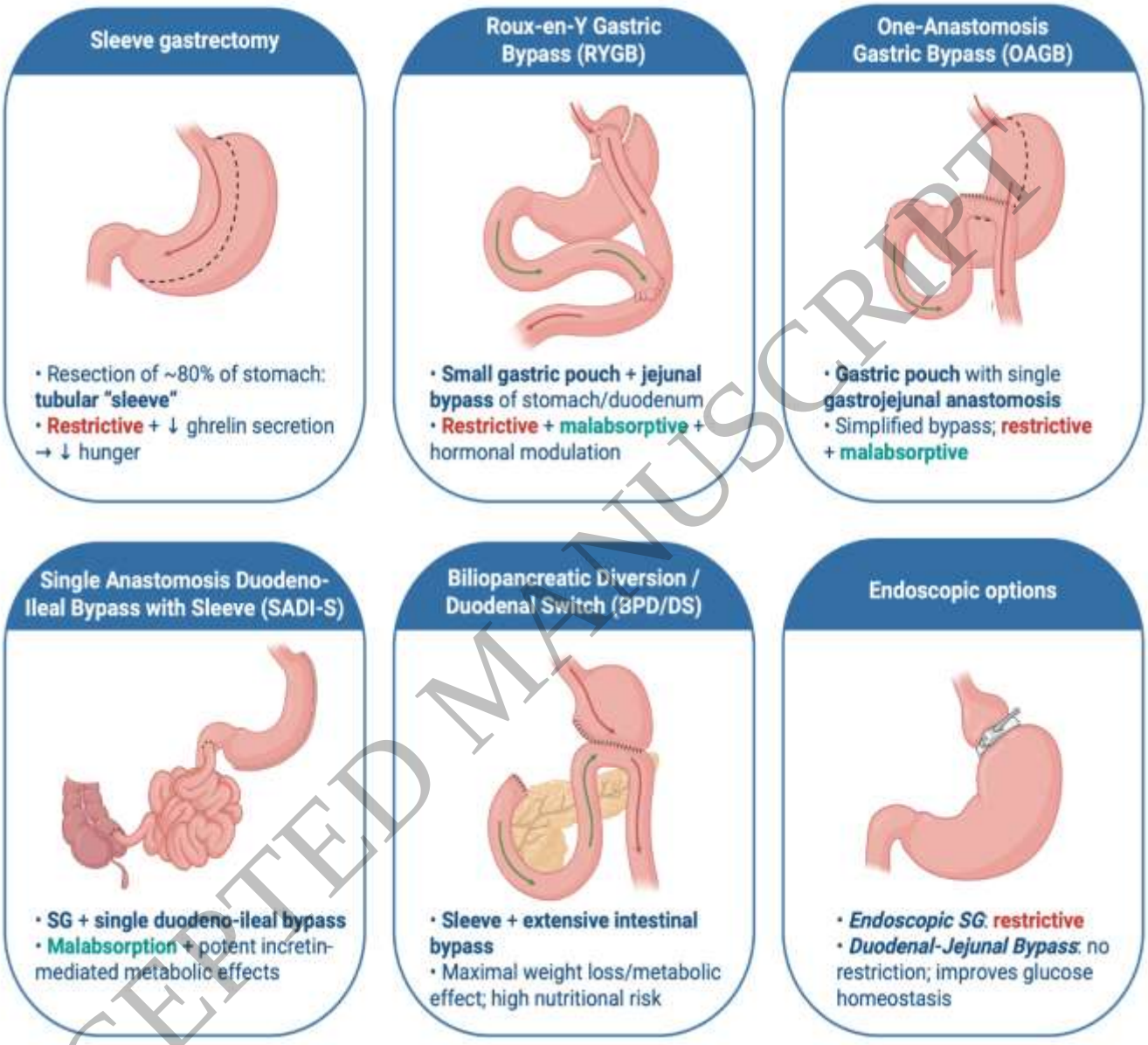

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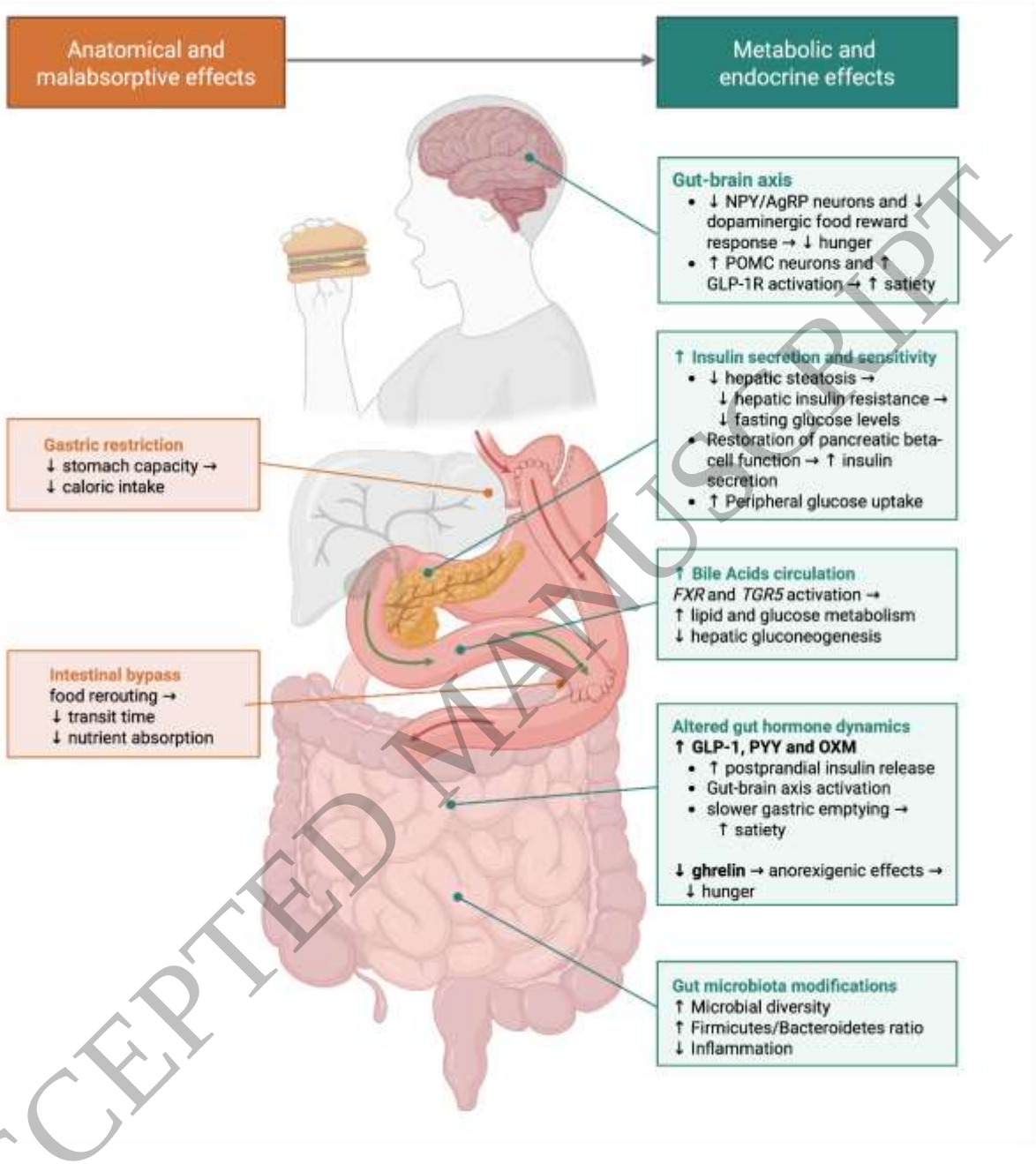

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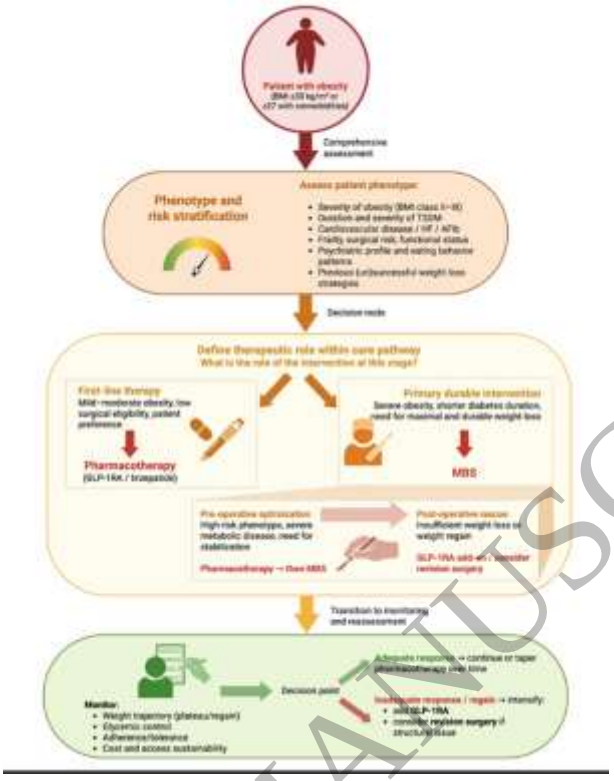

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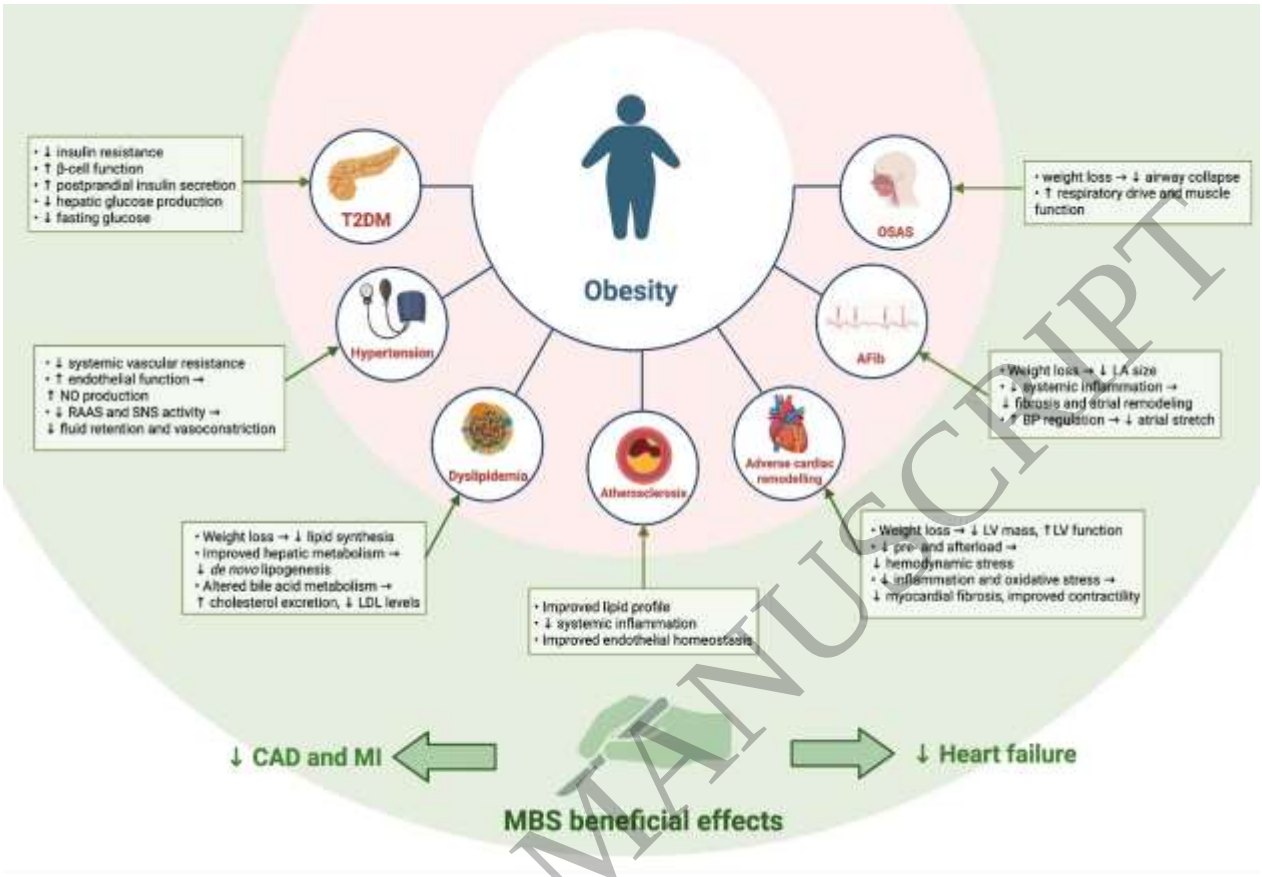

Graphical Abstract
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