

Bariatric and Metabolic Endoscopy: A New Paradigm

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The prevalence of obesity, type 2 diabetes mellitus, and metabolic syndromes is increasing globally. Minimally invasive metabariatric (MB) endoscopic therapies are adjunct treatments that can potentially bridge the gap between surgical interventions and medical therapy. A growing number of MB techniques are becoming available, allowing for more personalized and patient-targeted treatment options for specific disease states. MB techniques are less invasive than surgery and can precisely target different parts of the gastrointestinal tract that may be responsible for the pathophysiology of obesity and metabolic syndromes such as type 2 diabetes mellitus. These alternatives should be selected on an individualized patient basis to balance the expected clinical outcomes and desired anatomical targets with the level of invasiveness and degree of acceptable risk. Each MB intervention presents great flexibility allowing for a tailored intervention and different levels of patient engagement. Patient awareness and motivation are essential to avoid therapy withdrawal and failure. Differences between MB procedures in terms of weight loss and metabolic benefit will be discussed in this review, along with the insights on clinical decision-making processes to evaluate the potential of further evolution and growth of bariatric and metabolic endoscopy.

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INTRODUCTION

The gastrointestinal (GI) tract modulates nutrient absorption and glycemic control, releasing several important regulatory hormones (Figure 1) (1). Interestingly, different hormonal responses have been observed after common bariatric surgeries such as Roux-en-Y gastric bypass and sleeve gastrectomy. Roux-en-Y gastric bypass which bypasses the duodenum results in higher levels of glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and fibroblast growth factor-19 (FGF-19) compared with sleeve gastrectomy, which demonstrates higher levels of gastrin (Figure 2) (2). Different hormonal responses support the role of the GI tract in glucose homeostasis and metabolic control. Metabolic changes after bariatric surgery persist over time, and they are not merely associated with weight loss (WL), suggesting additional weight-independent mechanisms of hormone regulation and glycemic control (3–6). Surgical interventions targeting the stomach and small intestine can have a significant and durable impact on WL and type 2 diabetes mellitus (T2DM).

Surgical interventions offer a greater WL but potentially have a greater impact on patients in terms of their invasive nature, associated postoperative morbidity, and adverse events (AEs). However, although bariatric surgical interventions are proven to be effective, only 1% of eligible patients undergo surgery (7). On the other hand, medical, lifestyle, and pharmacological therapies are largely available and cost-effective but might fail to treat all patients, and compliance remains indifferent (8,9). The advent of metabariatric (MB) endoscopic interventions for bariatric and metabolic patients may bridge the treatment gap that exists between these therapeutic options, providing several minimally

invasive interventions that could optimize treatment (Figure 3). These MB endoscopic procedures present different levels of efficacy, durability, risk, and AEs (Table 1) but are being increasingly explored to tackle the growing global pandemic of obesity and metabolic syndromes.

Transmural and volume reduction therapies—procedures that result in high levels of total body WL

The following permanent or semipermanent treatments usually achieve high levels of total body WL (TBWL) involving all layers of the target organ, either creating an artificial transmural food passage or full-thickness plication. These may be justified when higher TBWL is aimed and when the alternative treatment with more invasive surgical intervention is less desirable.

Aspiration therapy

Aspiration devices reduce caloric intake by active aspiration of ingested food from the gastric cavity through an endoscopically placed percutaneous gastrostomy. AspireAssist (AA) (Aspire Bariatrics, Exton, PA) has been approved by the Food and Drug Administration (FDA) for treatment of class II and III obesity in patients failing conservative treatment. This device acts a long-term reversible treatment. Although active patient involvement has a possible negative impact on the quality of life, it allows for gradual therapy withdrawal. Thompson et al. (10) evaluated AA in a randomized controlled trial (RCT) on patients with a body mass index (BMI) of 35–55 kg/m². A total of 74% of patients who were on AA (82/111 patients) completed 52 weeks of treatment. Per-protocol

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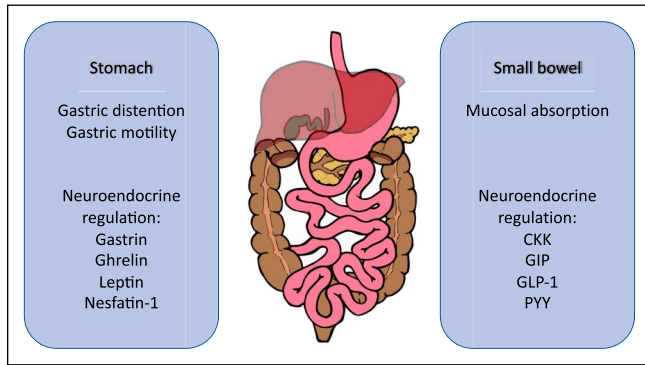


Figure 1. Mechanisms regulating food intake, nutrient absorption, and metabolic control originating from the gastrointestinal tract. The enteric nervous system, autonomic nervous system, and neuroendocrine cells can directly sense and regulate nutrients intake (i.e., orexigenic and anorexigenic hormones), as well as regulate nutrient metabolism with incretins (GLP-1 and GIP). GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

analysis showed a percentage of TBWL (%TBWL) of $>10\%$ in 70% of patients in the treatment group compared with 19% in the control group; the mean %TBWL was $14.2 \pm 9.8\%$ vs $4.9 \pm 7.0\%$, respectively. The serious adverse event (SAE) rate was 3.6% and included mild peritonitis, severe abdominal pain, and prepyloric ulcers likely related to mucosal contact of the intragastric portion of the gastrostomy tube. Several non-SAEs were reported, including peristomal granulation tissue (45%), abdominal pain (37%), nausea and vomiting (17%), peristomal irritation (17%), and infection (13%). Compared with controls, AA achieved glycated hemoglobin (HbA1c) reduction (-0.36% relative to 5.7% $P < 0.0001$) (10). A total of 58 patients continued the treatment beyond 12 months, and 15 patients concluded 4-year treatment showing sustained WL with an 18.7% TBWL on a per-protocol analysis (11). Similarly, data from a multicenter European registry showed that aspiration therapy provides sustained WL with a safety profile similar to percutaneous endoscopic gastrostomy (12).

Endoscopic gastroplasty

Endoscopic gastroplasty alters the anatomy and physiology of the stomach by plicating the gastric walls and reducing the

intra-gastric volume by up to 75%. The functional exclusion of part of the stomach results in a reduction of both gastric volume and motility (13). Two devices have been FDA-approved: the OverStitch (Apollo Endosurgery, Austin, TX) used for endoscopic sleeve gastroplasty (ESG) and Primary Obesity Surgery Endoluminal (POSE) (USGI Medical, San Clemente, CA) (14). Differences between these 2 techniques are shown in Figure 4. A meta-analysis published by Gys et al. (15) compared ESG vs POSE, where the percentage of excess WL (%EWL) was 68.3% vs 44.9% at 12 months. More recently, Lopez-Nava et al. (16) have modified of the POSE technique suturing the gastric body aiming to alter its motility (POSE-2). Their preliminary experience on 73 patients has shown a %TBWL of 15.7% at 6 months with no AEs. Further studies are needed to evaluate the efficacy of this technique compared with ESG and control groups.

A recent meta-analysis published by Khan et al. showed no significant WL difference between AA and endoscopic gastric plication (17). ESG has a significantly lower rate of AEs compared with laparoscopic sleeve (2.9% vs 11.8% , $P = 0.001$) and lower %TBWL at 12 months (17% vs 30.5% , $P = 0.001$) (18). The safety and efficacy of ESG were confirmed in 3 recent systematic reviews and meta-analyses, showing a %TBWL at 12 months between 16.1% and 16.5% with an SAE rate between 2.2% and 2.3% (19–21). WL at 24 months seems to be sustained with a %TBWL of 20.01% (21). Long-term data are promising, and abstract-based results presented by Hajifathalian et al. showed that 69% of the patients maintained a %TBWL $\geq 10\%$ at 60 months (22). Their quadratic regression models a maximum WL at 24 months. After achieving minimum weight, patients regained 2.4 kg–14% (22).

Other cardiometabolic effects of gastric plication were reported by Brethauer et al. (23). Metabolic parameters, including mean systolic and diastolic blood pressure, mean triglyceride and fasting insulin values, decreased by 15.2 mm Hg ($P = 0.0012$) and 9.7 mm Hg ($P = 0.0051$), 27.9 mg/dL and 4.5 $\mu\text{IU/mL}$, respectively. Sullivan et al. (24) published an RCT, including 332 patients with a significant decrease of both fasting glucose and low-density lipoprotein levels. Espinós et al. (25) showed improved glucose/insulin ratio, a postprandial increase of PYY, increased baseline ghrelin, and enhanced postprandial decrease. Interestingly, the gastric emptying time was longer at 2 months and returned to baseline at 6 months; this transient delay was associated with greater and sustained WL.

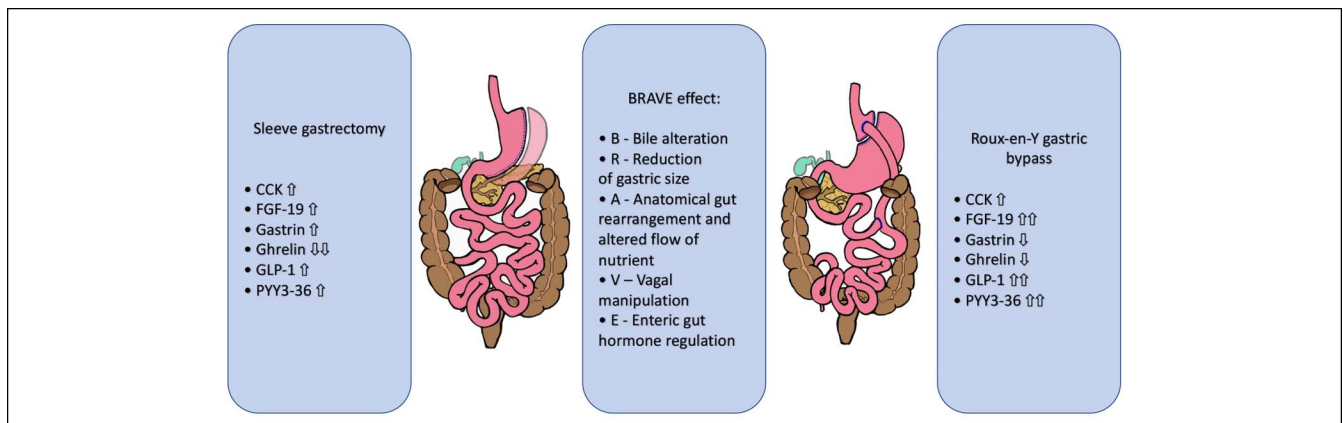


Figure 2. Effects of bariatric surgery (different hormonal changes after sleeve gastrectomy and Roux-en-Y gastric bypass). The BRAVE effects include bile flow changes, restriction of gastric size, anatomical gastrointestinal rearrangement, vagal manipulation, and enteric hormonal modulation. These changes induced by bariatric surgery are mimicked with endoscopic interventions.

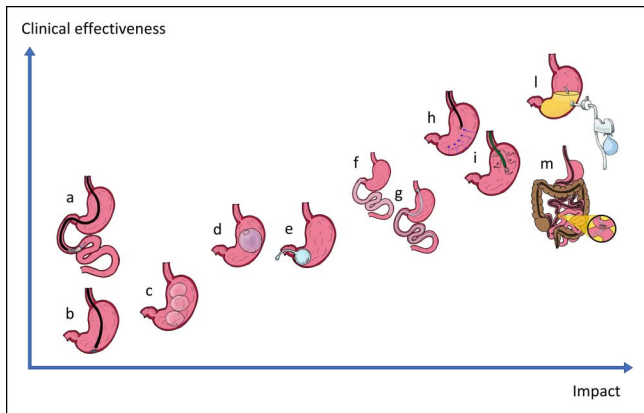


Figure 3. Endoscopic interventions for obesity and dysmetabolic conditions. Endoscopic interventions: (a) duodenal mucosa resurfacing, (b) intragastric botox injection, (c) gas-filled intragastric balloon, (d) liquid-filled intragastric balloon, (e) transpyloric shuttle, (f) duodenal-jejunal bypass liner, (g) gastro-duodenal-jejunal bypass liner, (h) endoscopic sleeve gastropasty, (i) Primary Obesity Surgery Endoluminal, (l) aspiration therapy, and (m) partial jejunal diversion.

Partial jejunal diversion

This device consists of 2 self-assembled magnetic rings that create an ischemic fistulation apposing side-by-side proximal and distal small bowel (Figure 3m). First-in-human (FIH) study on 10 patients has shown no device-related SAE, 14.6% TBWL at 12 months, and HbA1c reduction of 1.9% and 1.0% in diabetic and prediabetic patients, respectively (26). Few other data are available, and this device is not FDA-approved at present.

Endoluminal implantable therapies—procedures that result in lower levels of TBWL

These techniques use temporary endoluminal implants that achieve lower levels of transient and short-lived TBWL. They are less invasive but not necessarily safer. They target either the stomach or proximal small intestine. Their effectiveness can be increased by repeating or combining them together (27–29).

Intragastric balloons

Intragastric balloons (IGBs) have been the most widespread minimally invasive endoscopic intervention for WL. Several IGBs are available, each presenting unique features (30) (Table 2). A retrospective study comparing IGB with ESG showed a significantly lower %TBWL at 6 months (15.0 vs 19.5%, respectively) and 12 months (13.9% vs 21.3%, respectively) with higher AE rates of 17% vs 5.2%, respectively ($P = 0.048$) (31). A recent meta-analysis confirmed that IGB might be clinically inferior to EGS in terms of WL and AEs (32).

Most literature for liquid-filled balloons refers to Orbera (Apollo Endosurgery). Orbera achieved 11.27% TBWL (95% confidence interval, 8.17%–14.36%) at 12 months after implantation and a significant WL over controls (26.9% EWL; $P < 0.01$) as showed in the American Society for Gastrointestinal Endoscopy systematic review and meta-analysis, including 1,683 patients from 17 studies (33). Trang et al. reported a rate of nausea and vomiting of 63% and 55%, respectively, with the highest accommodative symptoms rate for Orbera compared with other IGBs (34).

Lower rates of explantation and intolerance can be obtained using gas-filled IGB, but this may compromise on WL (35). Indeed, in a recent meta-analysis, the gas-filled balloon does not achieve superior WL compared with lifestyle modification (36). Previously, Sullivan et al. conducted an RCT comparing Obalon, a swallowable gas-filled balloon and lifestyle therapy vs lifestyle therapy alone. Patients completing the treatment achieved a % TBWL of $7.1 \pm 5.0\%$ vs $3.6 \pm 5.1\%$ in the controls ($P = 0.0085$), and the SAE rate was 0.4%. At 48 weeks, 88.5% of the TWL was maintained (37). Over time, up to 3 balloons can be accommodated in the stomach to progressively reduce the volume of the gastric cavity.

Limited literature is available for other CE-marked IGBs that might present unique features. For instance, Elipse (Allurion, Natick, MA) is a swallowable liquid-filled balloon with a self-deflating valve mechanism with no endoscopy required; Spatz3 (Spatz, Fort Lauderdale, FL) is a liquid-filled balloon with adjustable volume and dwelling time up to 12 months. Retrospective studies and case series showed that down-volume adjustment might alleviate balloon intolerance, whereas up-volume adjustment may contrast the plateau effect facilitating additional WL (38–40) and provide a further delay of gastric emptying (41). A more recent, cross-sectional study showed that obese patients achieved greater WL with nonadjustable IGB, whereas overweight ($BMI > 27$) achieved greater WL with adjustable IGB (42). Additional prospective studies are needed to quantify the advantages of adjustable balloons in terms of WL and address safety concerns of catheter impaction as was seen in previous generations of devices (39,43).

In addition to WL, IGBs achieve other metabolic benefits. Popov et al. (44) published a large systematic review of 10 RCTs and 30 observational studies, including 5,668 patients, showing improvements in metabolic parameters that included fasting glucose, triglycerides, and diastolic blood pressure. In addition, Guedes et al. (45) reported a reduction of leptin, high-sensitivity C-reactive protein, glucose, insulin, and homeostatic model assessment of insulin resistance (shortly) with a concomitant increase of adiponectin/leptin ratio. Nguyen et al. (46) showed a significant reduction of alanine aminotransferase (ALT) and gamma-glutamyl transferase in obese patients with nonalcoholic steatohepatitis. A similar result was obtained by Folini et al. (47), showing liver steatosis reduction at magnetic resonance imaging. Bazerbachi et al. (48) reported a reduction of HbA1c ($1.3\% \pm 0.5\%$ $P = 0.02$), nonalcoholic fatty liver activity score, and liver fibrosis.

Transpyloric shuttle

The transpyloric shuttle (BAROnova) device consists of 2 silicon-based bulbs connected by a tether across the pylorus (Figure 3e). It intermittently obstructs the pylorus and delays the gastric emptying. Following initial safety concerns, it has been redesigned and is currently FDA-approved for a treatment period of 12 months (49). Marinos et al. (50) tested this device in an open-label trial of 20 patients assigned to 3- or 6-month treatment. The 6-month group achieved 14.5% TBWL. Overall, 10 gastric ulcers were noted; 2 required early device removal. More recently, a sham-controlled study was conducted by Rothstein et al. (51), where 270 patients were randomized in a 2:1 ratio to 12-month treatment or sham procedure. Abstract-based results showed 30.9% EWL in the treatment group vs 9.8%

Table 1. Endoscopic intervention for WL and dysmetabolic conditions

Name	Target	Availability and literature	Primary effect(s)	Metabolic effect(s)	Dwelling time	Advantage(s)	Disadvantage(s)	AE(s)
Intragastric balloon	Stomach	+++	Early satiety Delayed gastric emptying Possible hormonal	WL Hb1Ac reduction Improved liver tests	6–12 mo	Easy and widely diffuse Long-term experience Several different models with different features	Temporary effect with weight regain Patient compliance	Accommodative symptoms, balloon migration, obstruction, perforation, and pancreatitis
Endoscopic gastroplasty	Stomach	++	Early satiety Delayed gastric motility Possible hormonal	WL Improved glycemic control Improved lipid profile	Semipermanent	Flexible procedure allowing for different suturing patterns Longer effect	Complex procedure	Accommodative symptoms, perigastric collection, intragastric and extragastric bleeding, and hepatic abscess
Aspiration device	Stomach	+	Decreased caloric intake	WL HbA1c reduction	12–24 mo	Patient-controlled procedure	Patient-dependent aspiration	Fistula, buried bumper and infection
Transpyloric shuttle	Stomach	+	Transient pyloric obstruction	TBC	12 mo	Limited data	Limited data	
Botox injection	Stomach	+	Delayed gastric motility	TBC	N/A	Easy and widely diffuse minimally invasive	Temporary effect	
Duodenal bypass liner	Small bowel	++	Hormonal changes with restoration of incretin effect	WL HbA1c reduction Cardiometabolic marker improvement	12 mo	Rapid improvement of glycemic control	Complex procedure with safety profile concerns	Hepatic abscess, acute pancreatitis, bleeding, and perforation
Duodenal mucosal resurfacing	Small bowel	+	TBC	HbA1c reduction with improved insulin sensitivity Liver improvement	N/A	Limited data	Limited data	
Incisionless partial jejunal diversion	Small bowel	+	Enteric diversion	WL HbA1c reduction	N/A	Limited data	Limited data	

AE, adverse event; HbA1c, glycated hemoglobin; N/A, not applicable; TBC, to be confirmed WL, weight loss.

EWL in controls ($P < 0.0001$). Early device removal was required in 10.3% of patients, and the SAE rate was 2.5% (52).

Duodenal bypass liner

The duodenal bypass liners are impermeable sleeves interposed between the mucosa and GI lumen to impede nutrient digestion and absorption (Figure 3f–g). Currently, these devices are not FDA-approved. Most literature refers to EndoBarrier, a duodenal-jejunal bypass sleeve (DJBS) measuring 60 cm in length. During the placement, the self-expanding nitinol anchor is positioned into the duodenal bulb, and the impermeable fluorine polymer liner is deployed distally into the proximal jejunum. Similarly, ValenTx is a gastro-duodenal-jejunal bypass measuring 120 cm that is anchored to the gastroesophageal junction and

extends to the jejunum. This second device requires laparoscopic assistance for its placement (53,54).

An American Society for Gastrointestinal Endoscopy pooled analysis of 4 RCTs has shown significant WL difference compared with the control group (9.4% EWL; 95% confidence interval, 8.26–10.65). Notably, the duration of these studies was 12 and 24 weeks, which were shorter than the recommended dwelling time of 12 months. This analysis also showed significant HbA1c reduction compared with controls (33). The availability of alternative and highly effective medical therapy might not justify its use; however, DJBS has shown potential in improving metabolic parameters.

After DJBS implantation, a rapid improvement of T2DM and glycemic control has been noted as well as hormonal changes (55,56). Muñoz et al. (57) suggest additional weight-independent

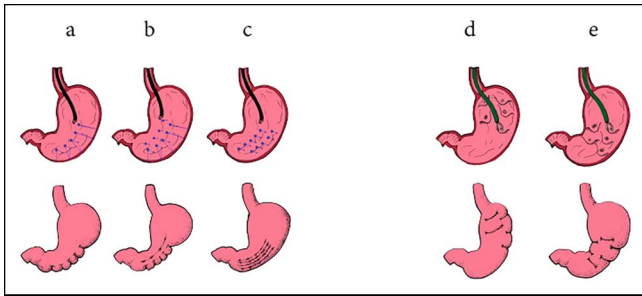


Figure 4. Endoscopic sleeve gastroplasty and POSE—illustration of different techniques and suturing patterns. On the left, endoscopic sleeve gastroplasty (a, b, c) suturing the antrum. Graus Morales et al. implemented a Z-pattern (c) instead of a triangular pattern (a, b). The Z-shaped running suture with multiple closer stitches aims to reduce suture tension and increase its durability (84). On the right, the POSE targeting the fundus (d), new suturing patterns targeting the antrum have been proposed by Lopez-Nava et al. POSE-2 (16) or distal-POSE by Jirapinyo et al. (85) (e). POSE, Primary Obesity Surgery Endoluminal.

mechanisms of glycemic control. Jirapinyo et al. (58) published a meta-analysis of 4 RCTs showing 1.3% HbA1c reduction, with a significant reduction by 0.9% compared with control. This reduction was sustained after 6 months. Pooled data from observational and RCTs showed a total WL of 18%, which remained significant after 1 year; GLP-1, PYY, and ghrelin increased, whereas glucose-dependent insulinotropic polypeptide decreased.

In addition, EndoBarrier improved liver enzymes (59,60) and liver elastography (61). van Nierop et al. (62) showed an increase of unconjugated bile acid and increase in GLP-1; similarly, Kaválková et al. (63) showed an increase of FGF-19 and bile acids with the restoration of postprandial peak of GLP-1 as well as an improved lipid and glucose regulation, and FGF-19 and GLP-1 can regulate lipid and glucose metabolism;

upregulation of this pathway might contribute to restoring the incretin effect, which is downregulated in dysmetabolic conditions.

Moreover, EndoBarrier placement reduced triglyceride to high-density lipoprotein ratio (64) and serum low-density lipoprotein levels (65). More recently, Roehlen et al. (66) showed improvement of other cardiovascular markers, including high-sensitive C-reactive protein, lipoprotein-associated phospholipase A2, and small dense lipoprotein fraction. Studies attempting to prolong metabolic benefits by increasing the implantation duration registered higher AE rate. The authors of both studies recommended an implantation time of 12 months (67,68).

This device still has safety concerns that need to be addressed. Betzel et al. (69) published a systematic review including 1,057 patients, 33 of which had an SAE rate of 3.7%, including 11 hepatic abscesses, 8 GI hemorrhages, 4 esophageal perforations, and 3 acute pancreatitis. Surgery was required in 8 patients, but no deaths were reported. Despite these risks, Laubner et al. (70) showed possible positive risk-benefit ratio in favor of DJBL for T2DM treatment.

Endoluminal non-device-based therapies—lower AE profile

The need for safer procedures has led to the development of less invasive, nonimplantable, and deviceless techniques. These focus on manipulation of the mucosal environment of the stomach and small bowel to achieve sustained benefits on metabolic control that are so intricately linked to the hormonal signals that this part of the GI tract regulates.

Intragastric injection

Botulinum toxin A (BTA) injection can temporarily inhibit gastric peristalsis. Conflicting evidence has been published on the efficacy of this intervention. Initial studies showed a delay in gastric emptying with WL without AE (71–73). In 2015, a meta-analysis of 8

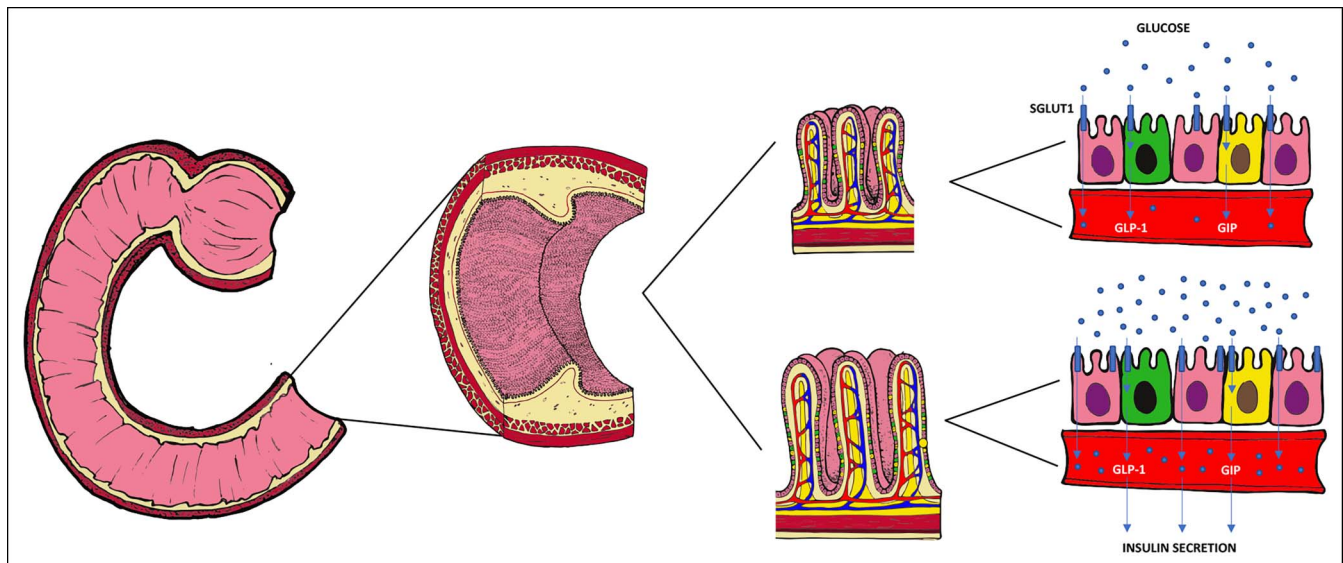

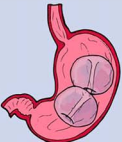




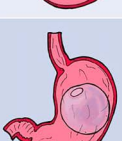




Figure 5. Mucosal alteration in dysmetabolic condition and westernized diet. Several mucosal alterations have been documented after chronic exposure to glucose and westernized diet (on the bottom) including increased barrier permeability, longer intestinal villi (86), increased expression of SGLUT1, as well as increased activity of sucrase and isomaltase (87,88). Mucosal changes involve L-cells (green) and K-cells (yellow) in terms of their number, ratio, and response to glucose stimulation. These cells regulate insulin secretion through incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) (86,89–91).

Table 2. Different types of intragastric balloons with their characteristics

Name	Illustration	Type Insertion Duration
FDA- and CE-approved intragastric balloon		
Orbera		Single liquid filled Endoscopic FDA: 6 months CE: 12 months
ReShape		Double liquid filled Endoscopic 6 months
Obalon		Up to 3 gas filled Swallowable with endoscopic removal 6 months
CE-approved intragastric balloon		
Heliosphere		Single gas filled Endoscopic 6 months
Spatz		Single liquid filled adjustable Endoscopic 12 months
Elipse		Single liquid filled Swallowable with self- deflated valve 4 months
MedSil		Single liquid filled Endoscopic 6 months
LexBal		Single liquid filled Endoscopic 6 months
End-ball		Single liquid and gas filled Endoscopic 6 months

studies concluded that BTA is effective in the treatment of obesity (74). Other data showed no impact on BTA injection on WL (75,76). More recently, 2 meta-analyses have concluded that intragastric injection of BTA is not effective (36,77).

Duodenal mucosal resurfacing

Duodenal mucosal resurfacing (DMR) is a novel procedure, which selectively ablates the duodenal mucosa and aims to revert mucosal changes present in T2DM (Figure 5).

Most literature refers to Revita (Fractyl Laboratories) (Figure 3a). This catheter creates a circumferential mucosal lift with submucosal injection followed by thermal mucosal hydroablation. Initial studies conducted on diabetic rats showed that duodenal mucosal abrasion reduces hyperglycemia. The same publication showed complete mucosal healing in a pig model treated with mucosal hydroablation after 6 weeks (78).

The FIH open-label trial evaluating safety and efficacy was conducted on a total of 39 patients; of which, 28 had long-segment ablation (average length = 9.3 cm), and 11 had short-segment ablation (average length = 3.4 cm). The pooled HbA1c reduction was 1.2% at 6 months ($P < 0.001$). The patients in the long-segment subgroup achieved greater HbA1c reduction compared with the short-segment group 2.5% vs 1.2% at 3 months ($P < 0.05$) and 1.4% vs 0.7% ($P = 0.3$) at 6 months. Within the long-segment group, patients with baseline HbA1c of 7.5%–10%, maintaining stable antidiabetic medications, achieved even greater HbA1c reduction ($1.8\% \pm 0.5\%$ at 6 months). Interestingly, HbA1c reduction was not significantly related to WL. Three patients experienced duodenal stenosis that was successfully treated with endoscopic balloon dilatation (79).

More recently, van Baar et al. (80) conducted a single-arm multicenter trial; in which, 9 of 46 patients were excluded from the final analysis because of technical failure. Per-protocol analysis on 36 patients showed $0.9\% \pm 0.2\%$ HbA1c reduction ($P < 0.001$) and liver enzyme improvement (ALT from $40 \pm 4\text{U/L}$ to $31 \pm 2\text{U/L}$). Changes were sustained and statistically significant up to 12 months. Once again, metabolic improvements were not related to WL. No DMR-related SAEs were reported. The same author published a pooled analysis of these 2 studies, showing a mean reduction of HbA1c of 1.1% at 6 months, with improvement in liver function tests, including ALT, AST, and fibrosis-4 index. Analysis of a subcohort of 14 patients showed additional metabolic effects at 3 months compared with baseline with improved mixed meal tolerance test and insulin sensitivity, improved lipid profile as well as a higher level of antioxidant and lower level of inflammatory molecules (81).

A multicentric RCT is currently evaluating comparative safety and efficacy. Abstract-based results showed a significant reduction of liver fat content measured with magnetic resonance proton density at 12 weeks as well as a significant reduction of HbA1c compared with the sham procedure (-0.6% [DMR] vs -0.3% [Sham]) at 24 weeks. Patients with baseline fasting plasma glucose $\geq 180\text{ mg/dL}$ achieved greater HbA1c reduction: -1.2% [DMR] vs -0.3% [Sham] [$P = 0.005$] (82).

The DiaGone (Digma, San Diego, CA) is a through-the-scope laser-based system for duodenal ablation. An FIH multicenter, open-label study is ongoing (NCT03390322).

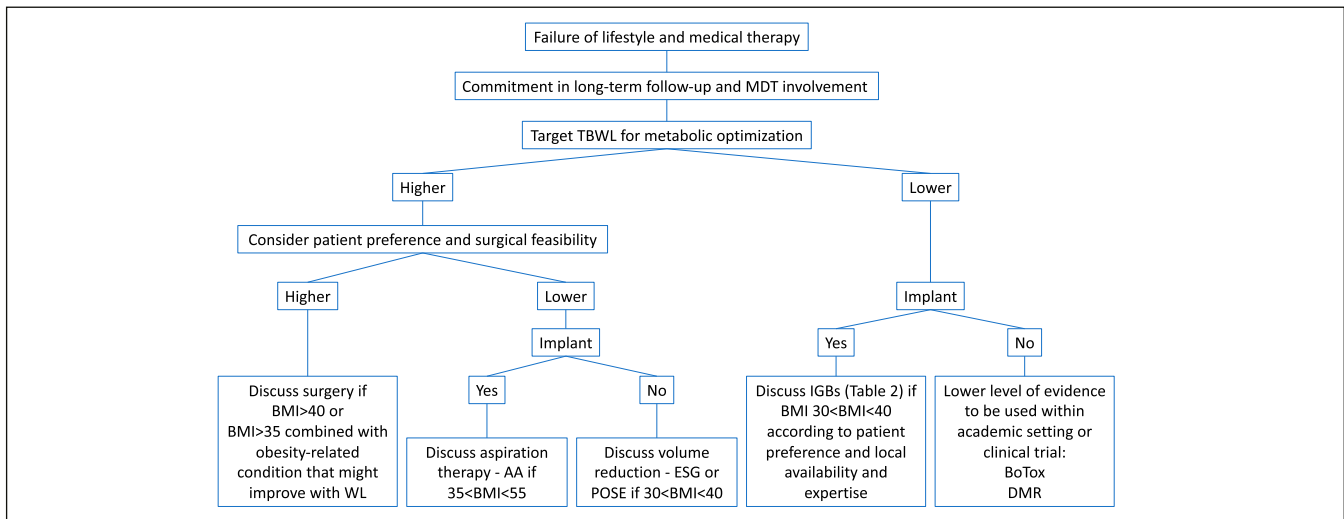


Figure 6. Decision-making algorithm guiding the choice among different MB interventions. Several medical and nonmedical aspects (i.e., adherence to postprocedure MDT follow-ups (92)) will likely play a crucial role in determining the success of the intervention and have to be evaluated for each single patient individually. MB endoscopic procedures should be particularly considered for patients with body mass index between 30 and 40 kg/m² who do not have other significant comorbidities. Those with a body mass index greater than this or with an obesity-related condition might be considered for surgery in the first instance because of the evidence of greater total body WL and resolution of comorbidities associated with obesity. Importantly, MB endoscopic procedures do not compromise the possibility of further bariatric surgery and, in most cases, are reversible and repeatable and can be used in high-risk patients with low risk of adverse events in expert hands (93). MB, metabariatric; MDT, multidisciplinary team.

Factors guiding clinical decision-making and role of multidisciplinary approach

MB procedural selection is a multifactorial decision process that should be performed on an individualized basis with a multidisciplinary approach taking into consideration several factors including fitness for surgery and anesthetic risk (i.e., comorbid or super obese patients), technical feasibility (i.e., frozen abdomen or anatomical variation), patient's preference and BMI, desired TBWL and metabolic endpoints, and reversibility of the intervention (i.e., younger patients). The willingness and appropriateness of implanting a device to support WL is another important factor to be evaluated. Those factors involved in the choice among surgical procedures and other MB endoscopic interventions are summarized in our proposed algorithm (Figure 6).

Among MB procedures, AA and endoscopic gastroplasty can ensure higher and sustained WL in a more consistent fashion. Those techniques are relatively newer and less widely available compared with IGBs. In particular, ESG and POSE require a higher level of technical skills and dedicated training to be performed, but adoption will grow with structured training and data. In addition, in those patients with a very high BMI who are not suitable for surgery, MB such as AA, IGBs, and endoscopic gastroplasty may also be used as a bridge to surgery or other endoscopic procedures that require a lower initial BMI.

Along with WL, other weight-independent benefits and indications for ESG (83), IGBs (44,48), and DMR are emerging including improved insulin sensitivity and improvement of liver pathology. Indeed, DMR and other techniques targeting the duodenum, once properly evaluated, could be introduced for DM2 and nonalcoholic fatty liver disease and favored for those patients with a lower BMI (80).

Implants may require a higher level of patient involvement, which may not be suitable for some patients. Of course, all techniques require patients' participation in postprocedure

dietary changes and follow-up visits, but this may be particularly important for implantable devices. For these reasons, a careful evaluation of patient's personality, attitude, and approach toward their condition as well as other social factors such as time availability and access to the center has to be taken into account.

A multidisciplinary approach should consider all these different aspects. Bariatric surgeons and endoscopists can evaluate the technical aspects of the procedures. The involvement of an obesity physician is preferred, although a physician with an associated specialty such as diabetes with a particular focus on obesity can be an alternative. Furthermore, dietitians, an anesthetist with experience of bariatric procedures, a psychologist, and specialist nurses all play important roles in the various aspects of these decisions. This is particularly important when considering the long-term follow-up of these patients including quality of life and ongoing dietary changes. This approach should be followed at all stages in the patient's care including before and after procedure.

CONCLUSION

MB endoscopic interventions could represent an alternative to surgery for treatment of dysmetabolic conditions. RCTs are needed to evaluate their long-term efficacy and exclude confounders for metabolic parameter improvement. Those results will help to position those techniques in the decision-making algorithm. Multidisciplinary decision-making on a per-patient level is key to the success of these innovations.

CONFLICTS OF INTEREST

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