

The evolution and current state of bariatric endoscopy in Western countries

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With the alarmingly increasing prevalence of obesity in the Western world, it has become necessary to provide more acceptable treatment options for patients with obesity. Minimally invasive endoscopic techniques are continuously evolving. Currently, metabolic and bariatric endoscopies encompass several different techniques that can offer significant weight loss and improvement in comorbidities with a favorable safety profile. Restrictive bariatric procedures include the use of intragastric balloons and gastric remodeling techniques with different suturing devices. Several studies have demonstrated the efficacy and safety of these techniques that are widely used in clinical practice. Small intestine-targeted metabolic endoscopy is an intriguing and rapidly evolving field of research, although it is not widespread in routine practice. These techniques include duodenal-jejunal bypass liners, duodenal mucosal resurfacing, and incisionless anastomoses. The aim of this review article is to provide a detailed update on the currently available bariatric endoscopy techniques in Western countries.

Keywords: Bariatrics; Gastrointestinal endoscopy; Obesity

INTRODUCTION

Obesity is a chronic relapsing disease characterized by a complex interaction between genetic factors and acquired environmental determinants. World Health Organization (WHO) has defined obesity as an excessive or abnormal fat deposition (body mass index [BMI] ≥ 30 kg/m²), capable of significantly impairing general body health.¹

According to the recent WHO estimate, in 2016, the preva-

lence of obesity among the world's adult population was 13%, while the prevalence of overweight and obesity among children and adolescents (5–19 years) had increased dramatically to >18%.¹

The primary goal of numerous obesity therapies is to achieve optimal results in terms of long-term weight loss. Non-invasive medical approaches (such as diet therapy, lifestyle modifications, and pharmacological therapies) often fail to achieve adequate and sustained weight loss. Although bariatric surgery is currently the most effective and durable therapy for morbid obesity, only approximately 1% of suitable patients undergo surgery, partly because of elevated costs and partly due to the potential for serious adverse events (SAEs) and mortality.²

The need to fill the huge gap between medical and surgical treatments for obesity has led to the development and widespread use of endoscopic bariatric treatments (EBTs), which provide minimally invasive and better procedural options when non-invasive approaches fail.³

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This review aimed to discuss and detail the current status of primary bariatric endoscopy in the Western world.

RESTRICTIVE ENDOSCOPIC BARIATRIC TREATMENTS

Intragastric balloons

Intragastric balloons (IGBs) are currently the most popular EBTs because of their minimal invasiveness, and good efficacy and safety.⁴ IGBs were first described by Nieben in 1982 and since then, evidence has accumulated over the years.⁴ IGBs induce satiety mainly by reducing the gastric volume, similar to an artificial bezoar, and by modifying stomach emptying.⁵ IGB placement is temporary and does not induce any permanent anatomical changes in the stomach. Indeed, IGBs must be removed after 4 to 12 months to minimize the risk of complications such as spontaneous rupture and migration, along with mucosal damage.⁴

Currently, several IGB models are available that vary in terms

of the insertion/removal procedure, filling medium, volume, and time of removal. However, only a few have received Food and Drug Administration (FDA) and/or European Community (EC) approval. The Orbera (Apollo Endosurgery), previously known as Bioenterics IGB (Inamed Corporation), was launched in 1991 and is currently the most investigated and used IGB in clinical practice. Currently, this is the only IGB proven to satisfy the Preservation and Incorporation of Valuable endoscopic Innovation thresholds of 25% excess weight loss percentage (%EWL) and 5% total body weight loss percentage (%TBWL) for both primary and non-primary EBT.³ The American Society for Gastrointestinal Endoscopy (ASGE) Bariatric Endoscopy Task Force conducted a systematic review and meta-analysis of 17 studies (1,683 patients), and reported %EWL and %TBWL of 25.44% (95% confidence interval [CI], 21.47%–29.4%) and 11.27% (95% CI, 8.17%–14.36%), respectively, 12 months after the placement of Orbera IGB.⁶ Characteristics of other IGB models and the main weight loss outcomes are summarized in Table 1.^{6–11}

Table 1. Intragastric balloons

IGB model	FDA/EC approval	Filling volume and medium (mL)	Placement	Removal	Time of treatment (mo)	Weight loss outcomes
ORBERA	FDA/EC approved	400–700 Saline	Endoscopy	Endoscopy	6–12	Abu Dayyeh et al. ⁶ (meta-analysis: 17 studies) • %TBWL 11.27% (95% CI, 8.17%–14.36%) at 12 mo • %EWL 25.44% (95% CI, 21.47%–29.4%) at 12 mo Kumar et al. ⁷ (meta-analysis: 44 studies) • %TBWL 13.2% (95% CI, 12.3%–14.0%) at 6 mo
OBALON	FDA/EC approved	250 (up to 3 balloons) Nitrogen gas	Swallowing	Endoscopy	6	Sullivan et al. ⁸ (RCT) • %TBWL 6.6%±5.1% at 6 mo • %EWL 23.9%±19.2% at 6 mo
HELIOSPHERE	FDA/EC approved	900–1,000 Air	Endoscopy	Endoscopy	6	De Castro et al. ⁹ (prospective study) • %EWL 27%±16% at 6 mo (no difference with fluid-filled bioenterics intragastric balloon)
SPATZ	EC approved	300–900 Saline (adjustable)	Endoscopy	Endoscopy	12	Abu Dayyeh et al. ¹⁰ (RCT) • %TBWL 15.0% (95% CI, 13.9%–16.1%) at 32 wk
ELIPSE	EC approved	550 Liquid	Swallowing	Spontaneous emptying and natural excretion	4	Vantanasiri et al. ¹¹ (meta-analysis: 6 studies) • %TBWL 10.9% (95% CI, 5.0%–16.9%) at 12 mo

IGB, intragastric balloon; FDA, Food and Drug Administration; EC, European Community; %TBWL, percentage of total body weight loss; %EWL, percentage of excess weight loss; CI, confidence interval; RCT, randomized controlled trial.

A few studies have evaluated weight loss after IGB, based on the obesity class. A study by Fittipaldi-Fernandez et al.¹² including 5,444 subjects who underwent 6-month IGB placement, reported a significant decrease in body weight, BMI, and excess weight during IGB treatment in all BMI groups. The mean %TBWL was similar across all groups: 16.32% in overweight, 17.96% in class I obesity, 18.35% in class II obesity, and 19.79% in class III obesity. However, the mean %EWL was different between the groups, being higher in overweight participants: 122.19% in overweight, 76.67% in class I, 56.01% in class II, and 45.45% in class III obesity. Other authors have reported a similar trend for %EWL, which may be due to the lowest excess weight at baseline in subjects with a lower initial BMI.^{13,14} Similarly, a study including 115 patients treated with swallowable IGB showed no statistically significant difference in terms of %TBWL at 6 months between patients with BMI 27.5 to 34.9 kg/m² and those with BMI 35 to 49 kg/m² (10.2% vs. 11.5%, $p=0.895$), while %EWL was significantly higher in those with a lower BMI (71.9% vs. 31.8%).¹⁵

A recent study including 1,100 subjects receiving a 12-month IGB treatment reported an overall median %TBWL of 11.11%. When evaluating weight loss outcomes based on BMI categories, the highest absolute weight loss was observed in subjects with BMI ≥ 45 kg/m² (13.61 kg; interquartile range, 6.35–20.19), while the highest %EWL was observed in patients with low BMI. However, no significant difference was found in %TBWL, which is consistent with previous studies.¹⁶

IGB treatment significantly improved obesity-related comorbidities. In a large Italian retrospective study including 2,515 subjects, IGB placement showed mean %EWL of $33.9\% \pm 18.7\%$ and improvement or resolution of obesity-related disorders (such as hypertension, diabetes, respiratory disorders, and dyslipidemia) in 44.6% of patients, with reduction of medications or shift to other therapies.¹⁷ Another study reported that 15% weight loss after IGB placement was associated with a significant improvement in obstructive sleep apnea.¹⁸ A recent meta-analysis of 40 studies (10 randomized controlled trials [RCTs], 30 observational studies, 5,668 subjects) evaluating the metabolic impact of IGB therapy showed improvement in most metabolic outcomes, including fasting glucose by -12.7 (95% CI, -21.5 to -4) mg/dL, glycated hemoglobin (HbA1C) by -1.1% (95% CI, -1.6% to -0.6%), triglycerides by -19 (95% CI, -41.6 to -3.5) mg/dL, diastolic blood pressure by -2.9 (95% CI, -4.1 to -1.8) mmHg, and waist circumference by -4.1 (95% CI, -6.9 to -1.4) cm.¹⁹ After IGB therapy, the odds ratios for

resolution of diabetes, hypertension, and dyslipidemia were 1.4 (95% CI, 1.3–1.6), 2.0 (95% CI, 1.8–2.2), and 1.7 (95% CI, 1.2–2.6), respectively. Another meta-analysis of 19 studies (911 subjects) evaluated the effects of IGB therapy on metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD).^{20,21} IGB treatment significantly reduced NAFLD activity score (NAS) by -3 (95% CI, -2.59 to -3.43), alanine aminotransferase (ALT) levels by -10.40 (95% CI, -7.31 to -13.49) U/L, aspartate aminotransferase (AST) levels by -10.68 (95% CI, -5.03 to -16.32) U/L, and liver steatosis (control attenuated parameter [CAP] via FibroScan) by -38.74 (95% CI, -21.59 to -53.92) dB/m.²⁰ Furthermore, IGB treatment induced significant improvement in insulin resistance assessed using the homeostatic model assessment for insulin resistance (HOMA-IR), which dropped by -1 . Weight loss and main metabolic outcomes are summarized in Table 2, along with those related to other EBTs covered in the following paragraphs.^{6,19–33}

As mentioned earlier, most of the published studies are on the Orbera balloon. Other balloons have been designed to overcome certain limitations of the Orbera, such as the high occurrence of maladaptive symptoms (such as nausea, vomiting, and epigastric pain) in the first weeks after placement and the need for early removal in approximately 7% of the patients.⁶ The meta-analysis by Trang et al.³⁴ (10 studies, 4 types of IGB, 938 patients) indicated that the rate of nausea and vomiting were 63.33% (95% CI, 61.49%–65.16%) and 55.29% (95% CI, 53.59%–56.99%), respectively, with the Orbera having highest rates. Air-filled and gas-filled balloons appear to be associated with better tolerability as the “feeling of a weight” in the stomach is reduced but at the expense of decreased weight loss.³⁴ For instance, unlike fluid-filled balloons, air-filled balloons are not associated with delayed gastric emptying.³⁵ Swallowable balloons were introduced to further minimize the invasiveness and costs of IGB placement and removal, thereby making these devices more appealing. The costs related to the endoscopic procedure and sedation for placement and removal cannot be regarded as an “absolute” limitation.⁴ In contrast, the inherent risk of bypassing endoscopic examination is not being able to identify gastric pathologies or contraindications, such as ulcers, large hiatal hernia, and previous gastric surgery.⁴ Placement of IGBs may lead to SAEs, including esophageal/gastric mucosal damage, perforation, gastrointestinal obstruction related to self-disinflation and migration, and spontaneous intragastric balloon hyperinflation, with an overall incidence ranging from

Table 2. Weight loss and main metabolic outcomes of endoscopic bariatric treatments

Procedure	Weight loss	Metabolic indexes	MASLD
Intragastric balloon	%TBWL: 11.27% (95% CI, 8.17%–14.36%) at 12 mo ⁶	Fasting glucose: –12.7 (95% CI, –21.5 to –4) mg/dL ¹⁹ HbA1C: –1.1% (95% CI, –1.6% to –0.6%) ¹⁹ Triglycerides: –19 (95% CI, –41.6 to 3.5) mg/dL ¹⁹ HOMA-IR: –1.73% (95% CI, –0.97% to –2.50%) ²⁰	NAS: –3 (95% CI, 0.259 to –3.43) ²⁰ ALT: –10.40 (95% CI, –7.31 to –13.49) U/L ²⁰ AST: –10.68 (95% CI, –5.03 to –16.32) U/L ²⁰ CAP score for hepatic steatosis: –38.74 (95% CI, –21.59 to –53.92) dB/m ²⁰
Endoscopic gastroplasty	%TBWL: 16.5% (95% CI, 15.2–17.8) at 12 mo ²² %TBWL: 17.2% (95% CI, 14.6–19.7) at 18–24 mo ²²	HbA1C: 5.5%±0.48% at 12 mo vs. 6.1%±1.1% at baseline, <i>p</i> =0.005 ²³ Triglycerides: 92.36±39.43 mmol/dL at 12 mo vs. 131.84±83.19 mmol/dL at baseline, <i>p</i> =0.02 ²³	NFS: –0.5 (95% CI, –0.80 to –0.19; <i>p</i> <0.01) ²⁴ HSI: –4.85 (95% CI, –6.02 to –3.67; <i>p</i> <0.01) ²⁴ ALT: –6.32 (95% CI, –9.52 to –3.11; <i>p</i> <0.01) U/L ²⁴ CAP score: 322.7 dB/m at baseline vs. 259.5 dB/m at 6 mo vs. 235.5 dB/m at 12 mo (<i>p</i> <0.001) ²⁵
The AspireAssist System	%TBWL: 12.1% at 52 wk ²⁶	Triglycerides –15.8 (95% CI, –24.0 to –7.6) mg/dL ²⁷ HbA1C: –1.3% (95% CI, –1.8% to –0.8%) ²⁷	AST: –2.7 (95% CI, –4.1 to –1.3) U/L ²⁷ ALT: –7.5 (95% CI, –9.8 to –5.2) U/L ²⁷
EndoBarrier	%TBWL: 18.9% at removal (8.4±4.0 mo) ²⁸ %TBWL: 7% at 1 year ²⁸	HbA1C: –1.3% (95% CI, –1.0% to –1.6%) ²⁸ HOMA-IR: –4.6 (95% CI, –2.9 to –6.3) ²⁸	Fatty liver index: 98.2 at baseline vs. 93.4 at explantation vs. 90.37 at 6 mo follow-up (<i>p</i> <0.001) ²⁹ NFS: 0.186±1.31 at baseline vs. –0.831±1.35 at removal (<i>p</i> <0.001) ²⁹ ALT: 29.03 UL at baseline vs. 42.29 U/L at removal, <i>p</i> <0.0001) ²⁹
Duodenal mucosal resurfacing	Mean weight loss: 1.84 kg (95% CI, –2.09 to 5.78); <i>p</i> =0.360) at 6 mo ³⁰	Fasting glucose –15.84 mg/dL at 6 mo ³⁰ Hb1Ac: –1.72% at 3 mo and –0.94% at 6 mo ³⁰	ALT: –10.82 U/L at 6 mo ³⁰ MRI-PDFF for hepatic steatosis: –6.59 at 6 mo ³⁰ FIB-4: 1.18 at baseline vs. 0.99 at 6 mo (<i>p</i> =0.001) score ³¹ Pilot trial of 11 patients with biopsy-proven NASH: no significant improvement in ALT, AST, FIB-4, NFS, vibration-controlled transient elastography, MRI-PDFF, HB1Ac, and HOMA-IR at 12 mo ³²
Incisionless Anastro-mosis System	%TBWL: 14.6% at 1-year follow-up ³³	HbA1C: –1.9% in diabetic patients ³³	N/A

MASLD, metabolic dysfunction-associated steatotic liver disease; %TBWL, total body weight loss; CI, confidence interval; HbA1C, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; NAS, nonalcoholic fatty liver disease activity score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, control attenuated parameter via Fibroscan; NFS, nonalcoholic fatty liver disease fibrosis score; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; FIB-4, fibrosis 4 index; NASH, nonalcoholic steatohepatitis; N/A: not available.

5.2% to 10.5%.^{34,36} According to a large meta-analysis (801 patients), the rate of SAEs was 5.24% (95% CI, 4.84%–5.64%).³⁴ However, the incidence of AEs is highly variable among studies due to several factors, including different sample sizes, variation in pharmacological protocols for antiemetic and pain medications, frequency of patient monitoring, as well as variability in reporting systems for the definition of “non-serious” and “serious” AEs.¹² Certain conditions may increase the risk of developing SAEs. For instance, Abu Dayyeh et al.⁶ reported that 50% of the perforations after Orbera placement occurred in patients who had undergone previous gastric surgery. Furthermore, exceeding the balloon dwelling time beyond the recommended

duration of therapy and underfilling the balloon may lead to migration, which may result in bowel obstruction or perforation.⁷ As such, proper and detailed collection of surgical history, endoscopic evaluation before balloon insertion, and following the instructions for balloon use are crucial for prevention of SAEs. Rare fatal events have also been associated with IGB placement.³⁷

With a focus on safety, absolute contraindications to IGB placement include active gastric, duodenal, or esophageal ulcers, any previous gastric surgeries, hiatal hernia ≥5 cm in size, gastric and esophageal varices, coagulation disorders, and anti-coagulant use as well as pregnancy, desire to become pregnant,

breastfeeding, alcoholism, and drug addiction. Relative contraindications include a large hiatal hernia measuring ≥ 3 cm in size, inflammatory bowel disease, previous abdominal surgeries, esophagitis, chronic nonsteroidal anti-inflammatory drug usage, and any prior uncontrolled psychiatric disorders.^{38,39}

Some studies have evaluated factors that may predict the success or failure of IGB placement with heterogeneous results. In a cohort of 277 patients, a high BMI and lack of assistance from a dietitian were independent risk factors of unsuccessful treatment for up to 12 months of follow-up.⁴⁰ Similarly, in another small series, BMI < 32 kg/m² and better adherence to dietitian counseling were associated with better weight loss at the 1-year follow-up.⁴¹ Furthermore, in a large study that included 583 patients, multivariate analyses showed that advanced age, female sex, basic educational level, and single or divorced marital status were the most powerful predictors of %EWL $\geq 50\%$ at the time of IGB removal.⁴² Dogan et al.⁴³ reported that in a cohort of 50 patients undergoing 6-month IGB treatment, %TBWL $\geq 5\%$ after 1 month of treatment may be a predictor of long-term (12–18 months) weight maintenance.

However, data on the long-term outcomes of IGB use, despite being scarce, show a trend toward weight regain over time. A cohort of 49 patients included in an RCT (6-month IGB vs. sibutramine) followed up for 10 years showed weight regain in both the groups, although the IGB cohort had an advantage compared to the control group at 5 years (-0.21 vs. 5.34 kg, $p < 0.01$) and 10 years (-2.32 vs. 0.03 kg, $p = 0.05$).⁴⁴ Notably, patients treated with IGB reverted to their baseline weight at 10 years. In a study including 500 subjects, Kotzampassi et al.⁴⁵ reported a %EWL of $42.73\% \pm 18.87\%$, $27.71\% \pm 13.40\%$, and $12.97\% \pm 8.54\%$ at 6, 12, and 60 months, respectively. Interestingly, patients who lost 80% of their total weight during the first 3 months of treatment succeeded in maintaining a %EWL $> 20\%$ at 1 to 2 years after IGB removal, which was attributed to the early agreement to multidisciplinary follow-up and maintenance of behavioral changes.⁴⁵ In summary, IGBs are currently widely employed in Western countries as a primary bariatric treatment for selected patients with overweight or obesity not fulfilling the bariatric surgery criteria, as well as a bridge-to-surgery for initial weight loss in patients with severe obesity and excessive surgical and/or anesthetic risk. However, the limited duration of treatment may be considered a drawback, as obesity is a chronic relapsing disease, although the repeatability and reversibility of IGB placement make it a versatile therapeutic strategy. Furthermore, the incidence of side effects was far from

negligible. Therefore, IGB treatment should be performed by experienced endoscopists at referral centers in a multidisciplinary setting, where proper selection and follow-up are warranted to optimize efficacy and safety. In this regard, preliminary esophagogastroduodenoscopy should be mandatory and not be an option.

GASTRIC REMODELING TECHNIQUES

Gastric remodeling techniques have gained popularity in the last decade as endoscopic restrictive procedures, and are currently widely performed in clinical practice. These techniques, which differ in the type of suturing device used, consist of full-thickness suturing of the gastric body, resulting in volume restriction and delayed gastric emptying.^{46–48} These events lead to alterations in the appetite pathway, and eventually, weight loss.⁴⁸ Gastric remodeling techniques are organ-sparing, scarless, reversible, and associated with a favorable safety profile; thus, they are attractive to both clinicians and patients.

Endoscopic sleeve gastropasty (ESG) was first described in 2013 and is performed with the OverStitch suturing device (Apollo Endosurgery), which is mounted over the scope and allows full-thickness sutures with the aid of a helix grasp.⁴⁹ The device was first developed for double-channel endoscopy (Fig. 1A).⁵⁰ Subsequently, a version of OverStitch Sx, usable with most single-channel gastroscopes, was introduced to promote wider accessibility to this technique (Fig. 1B).⁵⁰ ESG results in the tubulization of stomach (Fig. 1C).

To date, several studies have been published on ESG performed using the OverStitch Suturing System, which is approved by the US FDA and has a EC-marking. A systematic review and meta-analysis published in 2019 including eight relevant original studies (1,772 patients) showed a mean %TBWL of 16.5% (95% CI, 15.2%–17.8%) and 17.2% (95% CI, 14.6%–19.7%), at 12 and 18 to 24 months after ESG, respectively.²²

A milestone in supporting the efficacy of ESG is the Multi-center ESG Randomized Interventional Trial (MERIT).⁵¹ This trial randomly allocated 209 adults (1.5:1) with class I or II obesity to ESG with lifestyle modification or lifestyle modification alone (i.e., low-calorie diet and physical activity) groups. The ESG group showed a mean %EWL of 49.2% compared to 3.2% in the control group at 52 weeks ($p < 0.0001$). At the same time points, the mean %TBWL values were 13.6% and 0.8% for the ESG and control groups, respectively. Further, 68% of patients in the ESG group had a %EWL $\geq 25\%$ at 2 years follow-up, thus

adding evidence of durability of weight loss. Further, a prospective cohort study by Sharaiha et al.⁵² reported a mean %TBWL of 15.9% (95% CI, 11.7%–20.5%) at 5 years from ESG, with 90% and 61% of patients having a %TBWL >5% and >10%, respectively. Despite the limited number of patients ($n=68$), these results are encouraging as they support the long-term efficacy of ESG.

Although most current evidence on ESG involves patients with class I and class II obesity, few studies have evaluated its use in patients with class III obesity. In a retrospective study of 396 patients, ESG resulted in a significantly higher decline in TBWL, %TBWL, and BMI in class III obesity than that in class I and class II obesity at all time points, with %TBWL of 20.5%, 18.2%, and 16.5% in classes III, II, and I obesity, respectively, at 1-year post-ESG ($p<0.001$).⁵³ Similarly, another retrospective study including 1,506 patients with ESG showed that class III obesity was associated with a significantly higher mean %TBWL compared to lower obesity classes at all time points. At 24 months, patients with class III obesity showed a %TBWL of 20.4%, which was higher than those with class I (13.3%) and class II obesity (13.6%).⁵⁴ Moreover, a multicenter study reported mean %TWL rates of 8.91% in overweight, 13.92% in class I obesity, 16.22% in class II obesity, and 19.01% in class III obesity groups.⁵⁵ No differences were found in terms of AEs between the BMI categories.

ESG is associated with an improvement in obesity-related comorbidities. Sharaiha et al.²³ described a significant reduction in levels of HbA1C ($5.5\% \pm 0.48\%$ vs. $6.1\% \pm 1.1\%$, $p=0.005$), systolic blood pressure (122.2 ± 11.69 mmHg vs. 129.0 ± 13.4 mmHg, $p=0.02$), ALT (22 U/L vs. 42.4 U/L in men, $p=0.05$, and 20 U/L vs. 28 U/L in women, $p=0.01$), and serum triglycerides (92.36 ± 39.43 mmol/dL vs. 131.84 ± 83.19 mmol/dL, $p=0.02$)

when compared between 12 months after ESG and baseline. Alqatahni et al.⁵⁶ reported remission of hypertension (28/28), dyslipidemia (18/32), and diabetes (13/17) following ESG. This was confirmed by the MERIT, which showed that significant improvements in one or more metabolic comorbidities (such as diabetes, hypertension, dyslipidemia, and metabolic syndrome) and quality of life were achieved in the ESG group compared to lifestyle modification alone.⁵¹ A recent meta-analysis showed that ESG resulted in resolution of diabetes in 55.4% (95% CI, 46%–64%) of cases, resolution of hypertension in 62.8% (95% CI, 43%–82%), resolution of dyslipidemia in 56.3% (95% CI, 49%–63%), and resolution of obstructive sleep apnea in 51.7% (95% CI, 16.2%–87.3%) of cases.⁵⁷ A recent systematic review and meta-analysis of four observational studies (175 patients) evaluating ESG in the management of MASLD showed a significant improvement in liver parameters, such as NAFLD fibrosis score by a mean of 0.5, hepatic steatosis index by a mean of 4.85, and ALT by 6.32 U/L at 1 year following ESG (Table 2).²⁴

Another suturing technique to perform an ESG is the endomina triangulation platform (Endo Tools Therapeutics S.A.) and the related tissue apposition device (Transmural Anterior Posterior Endoscopic Suture [TAPES]), which obtained the EC-marking in 2015 for endoscopic suturing and in 2019 for endoscopic gastroplasty (Fig. 2).⁴⁶ The platform can be used with any standard gastroscope and can be easily assembled and disassembled from a scope within the stomach. TAPES consists of a single-use 5-Fr needle preloaded with sutures that are inserted and maneuvered through the angulated channel of endomina.⁴⁶ Starting from the incisura at the junction between the anterior wall and the greater curvature, the gastric wall is grasped with forceps and pulled back inside the platform, the needle preloaded with suture (bent at 90°) is passed through the

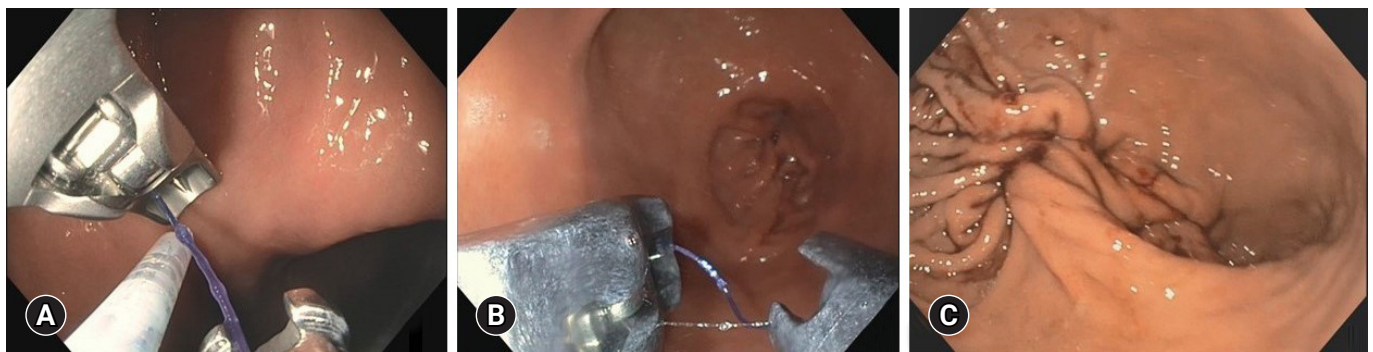


Fig. 1. (A) The OverStitch suturing system designed for double-channel gastroscope. (B) The OverStitch Sx suturing system designed for single-channel gastroscope. (C) Endoscopic appearance after endoscopic sleeve gastroplasty.

tissue, and the first tag with a knot is released. A second plication is then created at the opposite wall with the same TAPES with the release of a second tag. Eventually, the suture is tightened by grasping and pulling the knot with a snare. The same sequence is repeated multiple times along the gastric body, leaving the antrum and fundus free. The safety and efficacy of ESG with endomina is supported by a multicenter RCT including 71 patients (BMI, 30–40 kg/m²), which reported a mean %EWL of 38.6% in the endomina group, which was significantly higher than that in the control group (13.4%, $p < 0.001$).⁵⁸ Furthermore, the procedure resulted in a mean %EWL and %TBWL of 41.3% and 11.9%, respectively, at the 1-year follow-up.⁵⁸ A subsequent single-center RCT comparing three different suturing patterns showed no differences in weight loss, satiety, and gastric emptying modifications.⁵⁹ At the 12-month follow-up, the %EWL and %TBWL were 42.56% and 10.11%, respectively, for the whole cohort.⁵⁹

The primary obesity surgery endoluminal (POSE) procedure employs the Incisionless Operating Platform (USGI Medical).^{47,60} The system consists of a 54-Fr four-lumen tube (TransPort) equipped with a control handle enabling maneuvering in four directions. The four channels allow the insertion of an ultra-slim scope for intraprocedural vision, and specialized devices (g-Lix and g-Prox EZ) for grasping the gastric tissue, releasing tissue anchors, and cinching the sutures (g-Cath EZ). The device allows the creation of multiple full-thickness plications (Fig. 3). Initially, the POSE procedure involved the placement of plications at the gastric fundus to limit gastric accommodation. However, the unsatisfactory results of a blind RCT (ESSENTIAL trial), which showed a %TBWL of 5.0% at 1 year compared to 1.4% in the sham cohort, led to a shift in the plication target from the fundus to the gastric body, similar to other

existing gastroplasty techniques.⁶⁰ On average, approximately 20 plications are necessary to restrict and narrow the stomach.⁴⁷ In a multicenter study including 44 patients, the POSE 2.0 procedure resulted in 15.7%±6.8% of TBWL at 12 months along with improvements in lipid profile, liver biochemistries, and hepatic steatosis at 6 months.⁶¹ Furthermore, patients reported a significantly reduced maximum tolerated meal volume, increased fullness, and improved eating behavior at 6 months.⁶¹ In a recent prospective trial, the improvement in the CAP score and resolution of hepatic steatosis at 12 months was significantly higher in patients treated with POSE 2.0, than in those undergoing lifestyle modification alone.²⁵ In the POSE 2.0 group, the mean CAP score dropped from 322.7 dB/m at baseline to 259.5 dB/m and 235.5 dB/m at 6 and 12 months, respectively ($p < 0.001$). Conversely, the control group showed a mean CAP score of 338.6 dB/m at baseline, 326.8 dB/m at 6 months, and 320.9 dB/m 12 months ($p = 0.24$).²⁵

Currently available suturing devices are all manual; therefore, mastering these techniques requires a significant learning curve. Recently, an automated robotic suturing system (EndoZip™; Nitinotes) was developed as an easy-to-use device to overcome this limitation and standardize the procedure. A study using the first version of the automated device in 11 patients showed a mean TBWL of 16.2% at 6 months.⁶² Device technology has been further improved to achieve full automation and is currently under investigation in two pilot studies (NCT04773795 and NCT05623163).^{63,64}

Regarding safety, a meta-analysis including studies on ESG with OverStitch reported a 2.2% rate of SAEs, primarily pain and nausea requiring hospitalization (1.08%), including peri-gastric fluid collection (0.48%) and bleeding (0.56%).²² Storm and Abu Dayyeh⁶⁵ reported an SAE rate of 1.1% in more than 1,600 unique ESG procedures: intra-abdominal collection (0.4%), bleeding requiring transfusion or endoscopic interven-

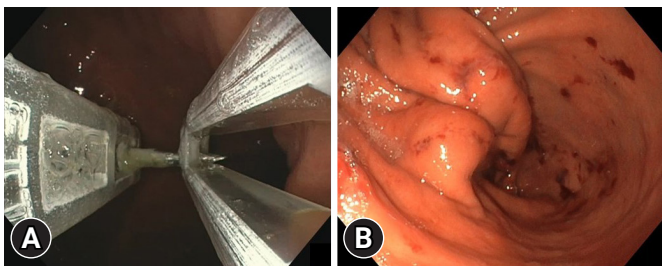


Fig. 2. (A) The endomina triangulation platform (Endo Tools Therapeutics S.A.) with the lateral arm bent at 90° in which the transmurals anterior posterior endoscopic suture is inserted (tip of the needle visible). (B) Endoscopic appearance after endoscopic sleeve gastroplasty with endomina.

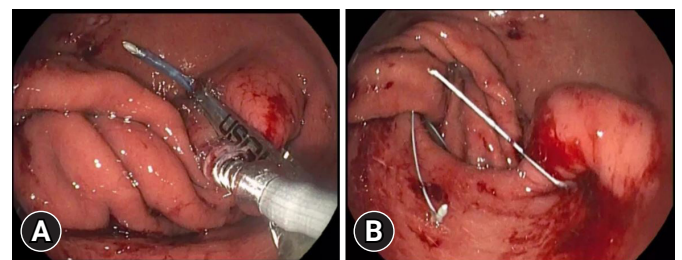


Fig. 3. (A) Primary obesity surgery endoluminal 2.0 (POSE 2.0) procedure. (B) Endoscopic appearance after POSE 2.0 procedure.

tion (0.4%), refractory accommodative symptoms requiring ESG reversal (0.2%), pneumoperitoneum and pneumothorax (0.1%), and pulmonary embolism (0.1%). Furthermore, the MERIT confirmed a favorable safety profile for ESG, with a procedure-related SAEs rate of 2% (3/131), including abdominal abscess, upper gastrointestinal bleeding, and malnutrition requiring ESG reversal.⁵¹ No mortality or need for intensive care or surgical interventions was reported.^{22,51,65} No SAEs have been reported in the studies evaluating gastric remodeling with endomina and POSE 2.0.^{58,61} However, it should be noted that most of the data on endoscopic gastroplasty concern cases performed with OverStitch, and no comparative studies between different suturing devices are available. However, because all these devices share the same basic principle of action (i.e., full-thickness suturing), gastric remodeling techniques should be contraindicated in cases of active gastric ulcers, congestive gastropathy, gastric polyposis (except for hyperplastic polyps), gastric or esophageal varices, and uncontrolled/untreated psychiatric disorders.⁶⁶

Some data suggest that ESG can be safely performed in adolescents and elderly patients with obesity. In a study by Alqahtani et al.,⁶⁷ 109 patients aged between 10 and 21 years (mean BMI, 33.0±4.7 kg/m²) showed a %TBWL of 16.2%±8.3%, and 13.7%±8.0% at 12 and 24 months after ESG, respectively, with no significant morbidity. In a recent retrospective study, we reported the use of ESG in 18 patients >65 years with obesity (mean BMI, 41.7 kg/m²) who achieved a median %TBWL of 15.5% (Q1–Q3, 10.5%–19.6%) at 12 months, and 15.5% (Q1–Q3, 9.6%–21.6%) at 24 months, along with significant improvement of obesity-related comorbidities and no SAEs.⁶⁸ However, these results should be further investigated in larger prospective studies. Some studies have investigated the predictive factors of success after ESG. Proper adherence to multidisciplinary follow-up has been reported to be a predictor of satisfactory weight loss at 1 and 5 years after ESG.^{52,69} Furthermore, younger age and early weight loss have been associated with better outcomes, suggesting that older patients and those with poor weight loss in the first months have a higher risk of long-term failure and thus may benefit from additional treatments and closer follow-up.^{23,52,55}

Long-term follow-up data on gastric remodeling techniques are still very limited, with only one published study with 5 years follow-up. Therefore, the predictive factors of success/failure and long-term outcomes should be further investigated in future studies.

Based on current evidence, the best candidates for endoscopic gastroplasty are adult patients with class I or II obesity who fail conservative weight loss methods, as stated in the recently published guidelines of the International Federation for the Surgery of Obesity and Metabolic Disorders.^{51,66,70} Furthermore, ESG is indicated for the management of adolescents with class II obesity.⁷⁰ However, ESG offers a therapeutic opportunity in patients with class III obesity who refuse surgery as well as poor surgical candidates, such as patients with surgically impenetrable abdomen due to previous surgery, and in patients with BMI ≥50 kg/m² as bridge-to-surgery.^{70,71}

Regarding the comparison between ESG and IGB, which are currently the most employed EBTs in clinical practice, data from literature suggest that ESG is superior in terms of the amount and durability of weight loss, with fewer AEs than that in IGB.⁷² A retrospective study comparing IGB and ESG showed a significantly lower %TBWL in the IGB cohort at 6 months (IGB, 15.0% vs. ESG, 19.5%) and 12 months (13.9% vs. 21.3%), and a higher rate of AEs (17% vs. 5.2%, *p*<0.048).⁷² A meta-analysis of 28 studies indirectly comparing ESG and IGB, confirmed that ESG is associated with greater weight loss compared to IGB, with a difference in mean %TBWL of 7.33% (95% CI, 5.22%–9.44%, *p*=0.0001) at 12 months.⁷³ Weight regain after IGB removal was indicated by a significant decrease in the mean %TBWL and %EWL after 18 or 24 months compared to 6 months.⁷³ The rate of SAEs were 1.52% and 3.97% for ESG and IGB, respectively, which meets the ASGE safety requirements.⁷³

THE ASPIREASSIST SYSTEM

The AspireAssist System (AA, Aspire Bariatrics) consists of a percutaneous endoscopic gastrostomy A-tube combined with a SkinPort and an aspiration tube which drains about 30% of ingested calories after meals.⁷⁴ AA was approved by the FDA in 2016 for patients aged ≥22 years with a BMI of 35 to 55 kg/m², after the failure of nonsurgical strategies.⁷⁵

An RCT (PATHWAY trial) showed a significantly higher weight loss in the AA group than that in the group with lifestyle modification alone, with a %TBWL of 12.1% vs. 3.5% at 52 weeks (*p*<0.001).²⁶

In a subsequent publication analyzing the long-term results of AA in 58 patients, the %TBWL and %EWL were 18.7% and 50.8% at 4 years, respectively.⁷⁶ A systematic review and meta-analysis of five studies (590 patients) reported significant improvement in several cardiometabolic parameters at 1 year,

including systolic blood pressure (-7.8 mmHg), diastolic blood pressure (-5.1 mmHg), triglycerides (-15.8 mg/dL), high-density lipoprotein (3.6 mg/dL), HbA1C (-1.3%), AST (-2.7 U/L), and ALT (-7.5 U/L)²⁷ (Table 2).

A subgroup analysis of two RCTs ($n=225$) showed that the AA group had a greater weight loss than controls by 11.6% ($6.5\%–16.7\%$) for %TBWL and by 25.6% ($16.0\%–35.3\%$) for %EWL, along with greater improvement in HbA1c (by 1.3% , $0.8\%–1.8\%$) and ALT (by 9.0 U/L, $3.9–14.0$ U/L).²⁷ Interestingly, another subgroup analysis of different age groups showed no differences in weight results following AA.²⁷ The pooled rate of SAEs was 4.1% , including buried bumper, peritonitis, severe abdominal pain, prepyloric ulcers, persistent fistulas, and product malfunction requiring A-tube replacement.²⁷ Contraindications to AA include active eating disorders (such as bulimia, binge eating disorder, and night eating syndrome), uncontrolled hypertension, certain types of previous abdominal surgery, pregnancy or lactation, inflammatory bowel disease, or stomach ulcers.

However, despite the promising results of AA, financial reasons led to its withdrawal from the market in February 2022.⁷⁷

SMALL INTESTINE-TARGETED ENDOSCOPIC BARIATRIC TREATMENTS

The small bowel plays a key role in metabolic homeostasis and pathogenesis of metabolic diseases and represents a potential therapeutic target.⁷⁸

Currently, available endoscopic bariatric procedures targeting the small bowel include bypass liners, duodenal mucosal resurfacing (DMR), and incisionless anastomosis. These treatments have been investigated extensively in several studies. However, none of these drugs are currently approved by the FDA.

DUODENAL-JEJUNAL BYPASS LINER

The duodenal-jejunal bypass liner (DJBL; GI Dynamics), also known as the EndoBarrier, is a 60 cm long fluoropolymer liner with a proximal self-expandable nitinol stent with spikes to anchor the device within the duodenal bulb.⁷⁹ The device is placed under both endoscopic and fluoroscopic guidance. A catheter-based delivery system is delivered over a guidewire into the duodenal bulb, and the liner is released, reaching the proximal jejunum at its distal end. As the liner is impermeable, contact between the nutrients and the mucosal surface of the proximal

small bowel is precluded, thus mimicking a surgical bypass.

The device is retrieved endoscopically 12 months after implantation. A meta-analysis of 14 studies and 412 patients with type 2 diabetes mellitus and obesity showed that EndoBarrier implantation for 8.4 ± 4.0 months resulted in a 1.3% reduction in HbA1C (95% CI, $1.0\%–1.6\%$) and a decrease of 4.6% in HOMA-IR (95% CI, $2.9\%–6.3\%$).²⁸ Interestingly, HbA1C was still below the baseline by 0.9% (95% CI, $0.6\%–1.2\%$) at 6 months after explant.²⁸ Regarding weight loss, at the time of removal, patients showed mean %TBWL and %EWL of 18.9% and 36.9% , respectively. One year after removal, weight loss remained significant, with a mean %TBWL of 7% and %EWL of 27.7% .²⁸

In a prospective study including 71 patients with obesity, diabetes, and NAFLD, EndoBarrier resulted in a significant reduction in fatty liver index from 98.2 at baseline to 93.4 at explantation and 90.4 at 6 months follow-up ($p<0.001$). Further, the procedure induced a reduction in the NAFLD score from 0.19 ± 1.31 at baseline to -0.83 ± 1.35 at removal ($p<0.001$), as well as a reduction of ALT levels (29.03 vs. 42.29 U/L, $p<0.0001$), which was maintained at 6 months follow-up (Table 2).²⁹

Despite its efficacy, the device did not obtain FDA approval and the EC mark was revoked because of the high incidence of liver abscesses (3.5%) in the randomized, sham-controlled pivotal trial (ENDO trial) that was prematurely suspended.⁸⁰ As liver abscesses have been recently found to be associated with proton pump inhibitors (PPIs) therapy, limiting their use during EndoBarrier may decrease the incidence of liver abscesses.⁸¹ A new System Pivotal Trial (STEP-1) using EndoBarrier is currently ongoing (NCT04101669) to further explore the safety and efficacy of this device.⁸² This trial had several exclusion criteria, including previous gastrointestinal surgery, anticoagulation therapy, history of abscess, active liver disease, active gastrointestinal ulcers, or other upper gastrointestinal bleeding conditions, and restriction in PPI use.

DUODENAL MUCOSAL RESURFACING

DMR employs a single-use balloon catheter Revita (Fractyl Health) placed under endoscopic and fluoroscopic guidance to induce hydrothermal ablation of the superficial mucosa of the duodenum (Fig. 4). Regeneration of the duodenal mucosa appears to disrupt pathways involved in the pathogenesis of type 2 diabetes mellitus and metabolic syndrome.³⁰

A meta-analysis of four studies and 127 subjects with non-in-

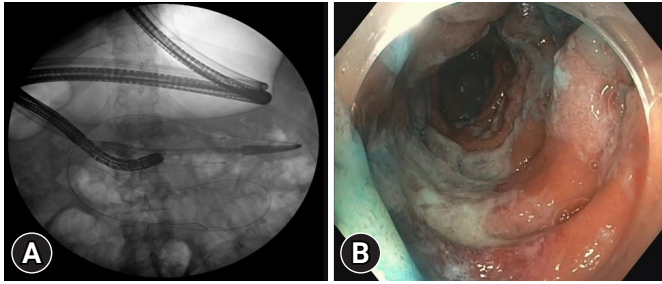


Fig. 4. (A) Fluoroscopic view of Revita (Fractyl Health) device. (B) Duodenal mucosal appearance after duodenal mucosal resurfacing.

sulin-dependent type 2 diabetes mellitus showed that the mean Hb1AC value decreased significantly by 1.72% at 3 months and 0.94% at 6 months after DMR.⁴³ Further, DMR resulted in a significant reduction in fasting plasma glucose (−15.84 mg/dL), ALT (−10.82 U/L), and hepatic steatosis assessed using magnetic resonance imaging-proton density fat fraction (MRI-PDFF) (−6.59) at 6 months follow-up.³⁰ However, no significant weight loss was observed. Regarding the possible impact of DMR on MASLD, a multicenter study including 85 patients with diabetes showed a significant reduction in ALT level (from 41±3 IU/L to 29±2 IU/L) and AST level (from 30±2 IU/L to 23±1 IU/L) at 6 months after DMR ($p<0.001$), along with a reduction in the fibrosis 4 index (FIB-4) score.³¹ However, a prospective pilot study including 11 patients with biopsy-proven nonalcoholic steatohepatitis (NASH) showed no resolution of NASH on biopsy at 12 months after DMR, and there was no significant improvement in serum aminotransferase levels, FIB-4 score, NAFLD fibrosis score, vibration-controlled transient elastography, MRI-PDFF, HB1Ac, and HOMA-IR.³² Therefore, the role of DMR in treating MASLD remains unclear (Table 2). Based on the exclusion criteria of available trials, the main contraindications to DMR include type 1 diabetes, history of ketoacidosis, history of severe hypoglycemia, previous gastrointestinal surgery, inflammatory duodenal disease, upper gastrointestinal bleeding, use of anticoagulant therapy, use of P2Y12 inhibitors and/or nonsteroidal anti-inflammatory drugs that cannot be stopped prior to DMR procedure, pregnancy, and active alcohol or substance abuse.^{83,84} Thus, DMR appears to be a safe procedure. The AEs were mostly mild and transient and included gastrointestinal symptoms, abdominal pain, and fever.^{30,83} Previously, three cases of duodenal stenosis 2 to 6 weeks after DMR were reported, all of which were effectively treated with endoscopic pneumatic dilatation.⁸⁵ This was attributed to overlapping ablation or ablation of the non-injected mucosa.

Following technical implementations, no similar events have been reported.

INCISIONLESS ANASTOMOSIS SYSTEM

The Incisionless Anastomosis System (GI Windows) is a technique aimed at creating an anastomosis using self-assembling magnets endoscopically placed into the proximal jejunum and terminal ileum. This procedure is more invasive and requires laparoscopic guidance and X-ray examination after 48 hours. Once the anastomosis is created by tissue necrosis, the magnets are eliminated through stools. A pilot study including 10 patients showed a %TBWL of 14.6% and a %EWL of 40.2% at the 1-year follow-up, along with a significant drop in Hb1AC in all diabetic (−1.9%) and prediabetic (−1.0%) patients.³³ No SAEs were reported. Notably, the anastomosis is not reversible, and no data are currently available regarding potential malabsorption in the long-term.

CONCLUSIONS

Obesity is a chronic, relapsing, and multifactorial disease requiring multidisciplinary and often multimodal management. Bariatric endoscopy has gained popularity in recent years as an effective, minimally invasive, and accessible interventional approach. Restrictive techniques are widely used in clinical practice in Western countries. However, data on long-term outcomes and predictors of success/failure remain limited, and further studies are needed.

Despite the promising results and fascinating nature of the available small intestine-targeted endoscopic bariatric and metabolic therapies, these should be further investigated and understood before being used outside the setting of clinical trials. Rapid and continuous advancements in this field suggest that bariatric endoscopy plays an increasingly important role in the management of obesity and its metabolic complications.

Conflicts of Interest

Ivo Boškoski is a consultant for Apollo Endosurgery, Boston Scientific, Nitinotes, Pentax, Cook Medical, Microtech, Erbe Elektromedizin, and Endo Tools Therapeutics S.A. Cristiano Spada is a consultant for Medtronic and AnX Robotics and received speaker fees from Olympus and Pentax. The other authors have no potential conflicts of interest.

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Author Contributions

Conceptualization: MVM, IB; Data curation: MVM, VB, VP, LG, GC; Supervision: CS, IB; Writing—original draft: MVM, VB, VP, LG, GC; Writing—review & editing: MVM, IB, CS.

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