



Endoscopic Procedures for Weight Loss

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Abstract

Purpose of Review To provide updated evidence on the endoscopic procedures for weight loss and to bring personal insights on the future of endobariatrics.

Recent Findings Intra-gastric balloons promote significant improvement in histologic and radiologic aspects of non-alcoholic steatohepatitis; the endoscopic sleeve gastropasty is effective up to 5 years and seems particularly beneficial to patients with BMI ≤ 40 kg/m²; distal POSE is a promising technique but still lacks adequate clinical data; aspiration therapy triggers remarkable weight loss, but data on weight trends after removal of the device are still lacking; the satiety-inducing device, the sleeveballoon, the gastric mucosal devitalization, and the endoscopic magnetic partial jejunal diversion are promising procedures still under study and refinements.

Summary Several therapeutic options are necessary during obesity's natural history. Therefore, endobariatrics should act in harmony with lifestyle interventions, diet modification, psychological treatment, pharmacotherapy, and bariatric surgery seeking the best outcome in the long term.

Keywords Endoscopy · Obesity · Overweight · Bariatric · Type 2 diabetes · Weight loss · Duodenal mucosal resurfacing · Jejunal diversion · Intra-gastric balloon · Duodenal liner

Introduction

The escalation of obesity has long become one of the worst pandemics human society has ever faced [1, 2]. Indeed, obesity is a silent, progressive, and relapsing disease that reduces both quality of life and life expectancy [3, 4].

Besides being a central risk factor for potentially lethal diseases such as acute myocardial infarction and cerebrovascular accident, it has also been identified as a predictor of poor COVID-19 outcomes [5]. That is probably due to the

overlapping of its inflammatory baseline condition and the virus-induced acute inflammatory syndrome [6].

The surgical treatment is the most effective therapy to address moderate and severe stages of the disease [7, 8]. However, there is an enormous gap between patients with an indication for surgery and patients undergoing treatment [9]. Furthermore, a non-negligible portion of patients suffers from excess weight and overweight-related comorbidities but do not reach formal surgery indications. Nonetheless, those individuals could still benefit from more conservative weight loss therapies.

Thus, less invasive alternatives to the operative modality are timely as they may extend the reach of bariatric therapy to unfit-for-surgery individuals. Endoscopic bariatric therapies (EBTs) are one such alternative that presented a rapid growth during the last decades. This article aims to discuss the most up-to-date evidence on EBTs and to bring personal insights on the future of the endobariatrics.

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New Data on Well-Established Procedures

Intra-gastric Balloons (IGB)

The IGB is the most ancient EBT. Drs Lloyd and Mary Garren firstly described an implantable gastric-occupying device in the early 1980s [10]. Since then, several refinements have

been made to the device, and there is sound evidence supporting the use of the available IGBs.

Currently, there are three Food and Drug Administration-approved (FDA-approved) balloons: the Orbera (Apollo Endosurgery Inc, Austin, TX, USA), the Obalon (Obalon Therapeutics, Carlsbad, CA, USA), and the Reshape Duo™. However, Apollo company purchased the latter one in 2018 and removed it from the market.

The Orbera is a liquid-filled 6-month or 12-month indwelling device and is most employed IGB worldwide. It has been marketed for more than 20 years in numerous countries and continents. That consistency allowed production and publication of reliable evidence, including a Brazilian consensus pooling experience from more than 40,000 procedures [11]. Several meta-analyses have already demonstrated the efficacy and safety of Orbera compared to placebo [12] and diet alone [13] in addressing severe obesity [14], obesity-related comorbidities [15], and non-alcoholic steatohepatitis (NASH) [16].

In the treatment of NASH, specifically, an interesting study recently demonstrated that a 6-month Orbera treatment leads to histologic and metabolic improvement. Twenty-one patients were enrolled and received preprocedural and postintervention liver biopsies and magnetic resonance elastography (MRE). Non-alcoholic fatty liver disease score (NAS) improved in 90% of patients. Fibrosis improved in 50% of individuals in MRE and 15% of histologic specimens. Mean serum liver enzymes also decreased significantly. Intriguingly, total body weight loss (TBWL) did not correlate with reductions in NAS and fibrosis [17•]. These data suggest an unknown positive effect of the IGB in NASH physiopathology that warrants further investigation. Finally, such a study led the FDA to grant Breakthrough Device Designation for Orbera IGB to treat NASH. That is particularly interesting as it will expand patients' access to endoluminal therapy.

Beyond organic improvement, Gadd et al. evaluated the impact of IGB treatment on mental health and quality of life. Pooling 9 different studies via meta-analysis with a total sample of 371 patients, the authors demonstrated a considerable improvement in the postprocedural quality of life. As to mental health, five studies were pooled and showed amelioration of depressive symptoms and anxiety [18•].

Concerning patient selection, Lopez-Nava et al. recently proposed a personalized approach based on preprocedural gastric emptying. Since one of the main mechanisms of action of the IGB is delaying gastric emptying, the authors hypothesized that patients with already delayed gastric emptying at baseline would have excessive adaptation symptoms. Contrariwise, patients with faster emptying would benefit the most from the therapy. The authors employed either baseline scintigraphy or a breath test and stratified the cohort of patients in quartiles. The findings corroborated this rationale: individuals in the lowest quartile had a 6-time higher likelihood ratio for intolerance leading to early removal. That result

may help determine which patient is unfit for IGBs. Additionally, individuals with delayed gastric emptying at 3 months lost significantly more weight at 6 and 12 months than patients with unchanged results. This finding confirmed that delayed gastric emptying is a critical weight loss promoter during IGB treatment. Also, it may be used as an early-on predictor of poor outcomes and may indicate the need for adjunct therapy in this subset of patients [19•].

The main drawback of the IGB treatment concerns durability. Even though long-term data are somewhat limited, a few studies reveal an overall trend towards weight regain after the IGB removal [20, 21]. Considering obesity is a chronic relapsing disease, one should not expect it differently as it may also happen after bariatric surgery [8]. Chan et al. recently published a 10-year data from a double-blind RCT. The initial trial compared IGB (Orbera balloon) plus placebo versus pharmacotherapy (sibutramine) plus sham procedure in non-morbidly obese individuals ($BMI < 35 \text{ kg/m}^2$) [22]. The authors reported a superior weight loss in the IGB group at 2 years, but no difference at 10 years. The groups only diverged in terms of willingness for further bariatric intervention, which favored the IGB (81% vs. 56%, $p < 0.01$) [23•].

Such data indicate that the benefit of IGBs is transient. Nevertheless, it carries adequate control and improvement of organic and mental comorbidities until the relapse occurs. That usually happens between the second and fifth postprocedural year. Since the therapy is repeatable, combinable, and allows sequential treatment, a personalized step-up approach might mitigate this durability shortcoming. Finally, the IGB does not preclude future bariatric procedures. On the contrary, it seems to stimulate the patient to undergo further intervention if needed. Those characteristics led the American Medical Association to designate a specific Current Procedural Terminology (CPT) code for the IGB in the USA, which will expand the clinical use of this device nationwide.

As to novel devices, the Elipse (Allurion Technologies, Wellesley, MA, USA) is a liquid-filled IGB that foregoes endoscopy for both implantation and removal. After 4 months in place, it deflates and passes naturally through the GI tract. Although it is not Food and Drug Administration-approved (FDA-approved) yet, the Allurion company recently announced the completion of its pivotal study and the premarket approval submission. As to medical data, a recent systematic review pooling more than 2000 patients demonstrated that the Elipse balloon promotes an average of 12% TBWL and 49% excess weight loss (EWL). There are also accompanying reductions in waist circumference and triglyceride levels [24]. This device could be revolutionary as it may reduce costs and substantially increase access to weight loss therapies.

The most common side effects of IGBs are nausea and vomiting, especially during the first 2 weeks—the adaptation period. Nausea occurs in approximately 2 out of 3 patients

undergoing treatment, and the majority of those also experience vomiting [25]. A combination of full-dose antiemetics is routinely recommended to avoid early removal. Ondansetron and dimenhydrinate are the central drugs in this context. More recently, the netupitant/palonosetron hydrochloride, a potent combination antiemetic drug commonly used to prevent nausea from chemotherapy, has also been shown efficacious in preventing nausea, vomiting, and gastric pain during the IGB adaptation period [26].

On the other hand, serious adverse events (SAEs) are rare but include gastric and esophageal perforations and small bowel obstruction due to migration. The clinical status at presentation should guide the decision between operative and non-operative management. If diffuse peritonitis or clinical instability is present, emergency surgery is needed. In the absence of those signs, one may attempt the non-operative management combining medications and local endoscopic treatment (closure for perforations, removal of migrated devices) [27].

TransPyloric Shuttle

The TPS (BARONova Inc, San Carlos, CA) has recently been approved by the FDA to treat adults with mild to moderate obesity. The device is composed of two smooth bulbs connected by a flexible silicone tether. After an endoscopic deployment, the large bulb attaches to the pylorus, while the small one hangs in the duodenum's descending portion. During the antral pump contractions, the TPS intermittently obstructs the gastric outlet, ultimately delaying gastric emptying and enhancing satiation.

An initial trial published in 2014 gathered data from 20 procedures in an open-label non-randomized study. At 3 months, patients experienced a mean %TBWL of $8.9 \pm 5.0\%$ and a mean % EWL of $25.1 \pm 14.0\%$. At 6 months, the mean %TBWL and %EWL rose to $14.5 \pm 5.8\%$ and $41.0 \pm 21.1\%$, respectively. As to safety, there were two cases of persistent gastric ulcers requiring early removal and additional 8 cases of asymptomatic ulcerations [28]. Such a high incidence of gastric ulcers fostered refinements in the device.

A large multicenter sham-controlled trial investigated the new version of the TPS, and the results led the FDA to approve it for clinical use. Two-hundred and seventy subjects (181 TPS and 89 control) were enrolled. Additional 32 individuals from the control group received TPS in the open-label phase after they were unblinded. At 12 months, the intervention group had higher %TBWL and BMI reduction compared to sham (9.5% [8.2, 10.8] vs. 2.8% [1.1, 4.5], $p < 0.0001$ and 3.5 vs. 1.01 , $p < 0.0001$). Nausea, vomiting, dyspepsia, and upper abdominal pain were present in more than 50% of treated subjects but were typically mild in severity. Twenty-one (10.3%) patients had at least one ulcer, and a total of 46 in the TPS group exited the study and had the device retrieved

before the 12-month follow-up. Nonetheless, the serious adverse events (SAEs) rate was considerably lower than the overall AE: 2.8%, among which gastric impaction was the most frequent event (1.97%) [29].

The TPS seems effective but still carries unpleasant and persistent symptoms during the treatment. This characteristic probably hampered the worldwide spread since its approval in 2019. Further refinements are warranted to grant this device a central role in the war against obesity.

Endoscopic Sleeve Gastroplasty (ESG)

Abu Dayyeh et al. firstly described the ESG in 2013 [30]. This procedure, also called “the Apollo method,” consists in employing a full-thickness endoscopic suturing device (Apollo Overstitch) to create apposition of the anterior, greater curvature, and posterior wall of the gastric body. The fundus remains intact and acts as a pouch with delayed emptying [31]. Since the first description in 2013, the ESG technique suffered several technical refinements. That includes using the helix to grasp tissue, per protocol CO₂ insufflation, increasing the number of bites per suture (from 6 up to 12), and adding reinforcement sutures in between the first suturing line [32]. With the current technique, the ESG has been proven reproducible and safe worldwide [33, 34], not only in academic centers but also in community health units [35]. A Brazilian consensus recently gathered 47 experts and provided practical guidelines to previously unattended technical and clinical issues related to the ESG [36]. Table 1 summarizes the main points of consensus in such a study.

Interestingly, although some authors recently described improved outcomes employing different suturing patterns [37], other data suggest that weight loss outcomes are unrelated to the suture pattern [38]. Still concerning technical refinements, Itani et al. proposed association with argon plasma coagulation to enhance fibrosis in the plication line, resulting in a superior sleeve-like lumen [39]. Albeit clinical data are lacking, the rationale seems appropriate as adequate endoscopic anatomy correlates with better outcomes during follow-up [40]. Nevertheless, one should expect that the imbricated gastric mucosal will eventually unfold. Pizzicannella et al. demonstrated that only 49% of ESGs were fully intact at a 6-month upper endoscopy [40]. Therefore, family history or individual increased risk of adenocarcinoma should not raise further concerns in the context of an ESG. Despite the mucosal unfolding, experts advocate that a fibrotic process in the gastric wall occurs secondary to the full-thickness stitching that permanently hampers gastric accommodation.

Several systematic reviews assessing the efficacy of the ESG were published in 2020. Due-Petersson et al. [41], de Miranda Neto et al. [42], Singh et al. [43], and Hedjoudje et al. [44], in four different articles, pledged the same: ESG is effective in the short-term and promotes average %TBWL

Table 1 Summary of practical recommendations to perform the endoscopic sleeve gastroplasty. Adapted from Galvao MG et al. [33]. *BMI* body mass index, *DVT* deep venous thrombosis, *CO₂* carbon dioxide, *ESG* endoscopic sleeve gastroplasty, *PPI* proton pump inhibitor**Indications**

- There is no age or BMI limit, but the minimum recommended BMI is 27kg/m²
- The ideal indication is for patients with grade I obesity (BMI 30–35kg/m²)

Contraindications

- Active gastric ulcers in the body or fundus, portal hypertensive gastropathy, gastric polyposis, gastric or esophageal varices, uncontrolled/untreated psychiatric disorders

Preparation

- Preoperative upper endoscopy and laboratory workup are mandatory
- DVT prophylaxis should be initiated according to clinical criteria
- A surgeon, a dietitian, and a psychologist should be part of the multidisciplinary team

Technique

- General anesthesia is mandatory
- Antibiotic prophylaxis is recommended
- CO₂ insufflation is mandatory
- Whether to perform stomach marking or not, the kind of suture pattern and the number of sutures employed are at the discretion of the endoscopist
- The main goal is to shrink the greater curvature, but the antrum should never be sutured
- Most endoscopists try to reduce the distal part of the gastric fundus
- ESG is eminently an outpatient procedure

Postprocedural care

- Recommended symptomatic drugs: PPI, ondansetron, hyoscine/scopolamine, steroid (dexamethasone), analgesics
- PPI should be maintained for 1–3 months

up to 20% at 24 months. Although controlled studies are still lacking, the consistency of their findings indicates that the demonstrated efficacy is reliable.

As to original data, Sharaiha et al. published a recent study showing 5-year outcomes of the ESG to treat obesity. From a series of 216 patients, 38 were eligible for a 5-year follow-up assessment. Among them, 18% were lost to follow-up. The remaining individuals presented a mean %total body weight loss (%TBWL) of 15.9% (95% CI, 11.7–20.5). Sixty-one percent of patients sustained at least 10% TBWL at 5 years. Although it is small-sampled, this study suggests that ESG outcomes are also durable in the long term [45••].

Concerning new indications, another recent study investigated the effect of ESG on obesity in children and adolescents. Alqahtani et al. reported a series of 109 consecutive mildly obese patients aged 10 to 21 years old undergoing ESG. At 12 and 24 months, the mean %TBWL was 16.2% ± 8.3% and 13.7% ± 8.0%, respectively. Fourteen patients (12.8%) required ambulatory visits for analgesia, and one underwent endoscopic removal of the stitches due to refractory abdominal pain. However, there were no emergency admissions, deaths, or significant morbidity. This data suggest that ESG is also effective and safe to treat young individuals suffering from obesity [46].

Another recent article assessed the impact of adjunct pharmacotherapy with liraglutide. This glucagon-like peptide-1 agonist amplifies insulin secretion, delays gastric emptying, and upregulates satiety by a central effect on the

hypothalamus [47, 48]. In an international cohort study, Badurdeen et al. employed a propensity score analysis to match 26 patients receiving GLP-1 at month 5 after ESG to 26 individuals declining it. At 12 months (7 months after introducing pharmacotherapy), patients from the GLP-1 group presented superior weight loss and greater reduction in percent body fat [49••]. This study is of paramount importance as it proves synergism between endoscopic and pharmacological approaches. Possibly, the combination of such therapies will become the standard of care soon.

Finally, one of the potential negative implications of the ESG would be increased surgical risk due to peritoneal adhesions and gastric imbrication. Although the need for rescue bariatric surgery after ESG is negligible—around 0.8%—surgical conversion had not been proven safe until recently [50]. Two studies demonstrated that a previous ESG does not pose substantial technical issues to a surgical conversion. That applies to Roux-en-Y gastric bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG) [51, 52].

As to comparative data, interesting articles have already been published, but most are non-controlled and non-matched retrospective cohorts. Non-matched studies frequently present groups with unbalanced baseline characteristics due to the intrinsic selection bias [53–55]. Dissimilar demographics handicaps interpretation of outcomes. One such study recently demonstrated that ESG is superior to IGB in weight loss, but baseline data typically differed between groups [56].

Consequently, some authors have employed case-matched designs to mitigate the negative impact of selection bias. In this sense, a case-matched cohort comparing ESG to high-intensity diet plus lifestyle therapy recently showed that the former promotes more significant weight loss within 12 months [57].

As to comparison against surgery, another case-matched study with 137 patients compared the LSG to the ESG. The authors demonstrated that the LSG carries superior weight loss at a 6-month follow-up ($23.6\% \pm 7.6\%$ vs $17.1\% \pm 6.5\%$, $p < 0.01$). Conversely, it also poses a higher risk for adverse events (AEs) and new-onset GERD (16.9% vs 5.2% , $p < 0.05$ and 14.5% vs 1.9% , $p < 0.05$, respectively) [58].

Finally, Marincola et al. compared those modalities through a meta-analysis design and confirmed that the surgical approach is superior in weight loss. However, no head-to-head study was included as few cohorts, and no controlled studies comparing those two modalities were available [59]. Moreover, another meta-analysis demonstrated identical results, but the limitations persist as they are related to the literature itself and not to the methodology of the study [60].

Arguably, endoscopic and surgical sleeves fit better to different types of patients, which explains the absence of comparative head-to-head studies. Instead, future controlled trials should focus on assessing the efficacy and safety of those strategies according to the severity of obesity. In overweight and mild obesity, one should compare ESG to non-operative modalities (e.g., IGB, diet, medications). In class II patients, ESG should be tested against LSG. However, current data allows anticipating the inferiority of ESG in terms of weight loss and durability for class III obesity [54, 58]. Considering the evident benefit of bariatric surgery for severe obesity [8] and the high cost added to the complex logistics of conducting an RCT [61], one might not need to test ESG against LSG for class III individuals. In this situation, current non-comparative data already support ESG for patients declining or unfit for surgery [62].

Pose and Pose 2.0 (Distal POSE)

The primary obesity surgery endoluminal (POSE) involves the employment of the Incisionless Operating Platform (IOP) (USGI Medical, San Clemente, CA, USA). The IOP is a 4-component device that allows endoscopic control of a full-thickness plication system. It delivers sequential anchors in the stomach to promote gastric imbrication [63].

The initial technique proposed impairing gastric accommodation by shrinking the fundus. Several non-controlled studies demonstrated the efficacy and safety of the POSE procedure [64, 65] and led to the development of a large sham-controlled trial. The ESSENTIAL trial, however, failed to demonstrate the long-term efficacy [66].

This failure was credited to technique and not to the device itself, which prompted modifications in the plication sequence. Instead of focusing on the fundus, the new technique, called distal POSE or POSE 2.0, aims to reduce gastric volume and alter motility. The operator creates two transverse plication rows, one in the distal body and the other in the proximal body. Then, they are connected through two longitudinal rows, one in the anterior and the other in the posterior wall. The transverse rows are the belts, while the longitudinal rows are suspenders [67]. The final aspect reduces the gastric length and alters the motility of the stomach [68].

Two case series describing the distal POSE have been published to date. Jirapinyo et al. reported results from 10 subjects undergoing this novel procedure. All patients received the distal POSE with an average of 21 ± 4 plications per case and experienced a mean shortening by 11.0 ± 5 cm in the gastric body. There were no SAEs. At 6 months, the mean %TBWL was $15.0\% \pm 7.1\%$, and 8 patients (80%) presented at least 25% EWL [69]. Lopez-Nava et al. reported outcomes of 46 patients at 1 year. Mean %TBWL was $17.8 \pm 9.5\%$, and BMI reduction was 7 ± 4.3 kg/m². Interestingly, endoscopy at 12 months showed intact sutures and sustained reduction in gastric length compared with baseline (26.9 ± 5.3 cm vs. 35.7 ± 3.5 cm, $p < 0.001$) [70].

The distal POSE seems promising, but open-label followed by sham-controlled trials are warranted to confirm such high expectations. In the meantime, physiology studies could provide valuable information on how POSE 2.0 promotes weight loss. That information would allow better patient selection and even further refinements in this still-evolving technique.

Aspiration Therapy

The AspireAssist™ is a novel FDA-approved device for the treatment of obesity. The index procedure is similar to a standard percutaneous endoscopic gastrostomy. The gastric portion of the device is a thick multi-fenestrated tube (A-tube) directed to the fundus. The outer part is a button-like implant that attaches to an external portable aspiration machine. After eating, the patient aspirates and disposes of around 30% of the ingested food [71]. Adjunct lifestyle interventions and nutritional counseling are also recommended as in all obesity-directed therapy.

The PATHWAY trial, a large open-label multicenter study, enrolled 171 patients to compare the aspiration therapy ($n=111$) versus lifestyle counseling ($n=60$). At 12 months, the mean %EWL and %TBWL were $31.5 \pm 26.7\%$ and $12.1 \pm 9.6\%$, respectively, in the intervention group versus $9.8 \pm 15.5\%$ and $3.5 \pm 6.0\%$ in the control group ($p < 0.001$). Aspiration patients also presented significant reductions in triglycerides, HbA1c, low-density lipoprotein, systolic and diastolic blood pressure, and an increase in high-density cholesterol. The SAEs rate was 3.6% (4/111) and entailed severe

abdominal pain, peritonitis, gastric ulcer, and port malfunctioning requiring tube replacement [72]. Among the 111 individuals from the aspiration group, 58 continued in the study for a 4-year evaluation. Interestingly, the patients presented a progressive weight loss throughout follow-up: 14.2%, 15.3%, 16.6%, and 18.7% TBWL at 1, 2, 3, and 4 years, respectively ($p < 0.01$). There were two persistent fistulas (2%) requiring surgical repair after tube removal [73].

The low rate of persistent fistula contradicts data from a post-market European registry study published in 2018. Despite similar weight loss throughout a 4-year follow-up, Nystrom et al. reported four such cases among the 47 removals (8.5%) and suggested that the risk escalates after 2 years post-gastrostomy. Additionally, there were 12 cases of gastric leakages and several other device-related adverse events (stomal irritation/granulation tissue, infection, buried bumper, and tube malrotation) [74].

Such data suggest that the AspireAssist™ is effective in the short term, but unwanted complications arise in the long term. Undoubtedly, aspiration is not a definitive therapy, and information on clinical management after device removal is lacking. Furthermore, the ideal indwelling period remains unknown. Future studies should focus on filling those gaps to minimize adverse events and exploit the therapy to its best.

Upcoming Procedures

Intragastric Satiety-Inducing Device (Full-sense®)

The Full-sense® device (FSD) (Baker, Foote, Kemmeter, Walburn, LLC, Grand Rapids, MI, USA) resembles a metallic esophageal stent attached to a wide transversal disk. The operator deploys the FSD at the esophagogastric junction through an upper endoscopy and under fluoroscopic control. The tubular part is the esophageal side, and the disk is the gastric side of the device.

The FSD is capable of applying continuous pressure to the EGJ while distending the gastric fundus. Consequently, it may stimulate vagal afferent receptors to induce satiety [75] and downregulate circulating ghrelin, thus alleviating hunger [76, 77].

Three animal studies concerning the FSD have already been published, and the first-in-human study is currently ongoing in India. Initially, Park et al. [78] and Luo et al. [79] investigated different types of devices to reduce the high migration rates. Their results supported the third animal study that focused on the efficacy and physiology of weight loss. Bakheet et al. implanted the FSD in 5 juvenile pigs and compared them to three control ones. Despite previous refinements in the device, the migration rate was still 40% (2/5). The intervention group presented lower weight gain rates compared to the control group during a 6-week follow-up.

Moreover, pigs receiving the FSD presented lower ghrelin levels and fewer gastric interstitial cells of Cajal in a microscopic post-mortem examination. This latter finding suggests that the FSD might also alter gastric motility, eventually improving weight loss [80].

Sleeveballoon

The Sleeveballoon consists of an intragastric balloon attached to a duodenal liner. The balloon occupies 2/3 of the gastric chamber, while the liner bypasses the duodenum as it delivers food directly to the mid-jejunum. The device mimics of the surgical RYGB effect by combining restriction, malabsorption, and hormonal changes.

An animal study assessing the physiology and metabolic effect of the Sleeveballoon has already been published. Casella-Mariolo et al. developed a three-group study involving 30 rats undergoing RYGB, Sleeveballoon, or a sham operation. Rats from both Sleeveballoon and RYGB groups presented sustained weight loss and similar improvement in hepatic and whole-body insulin sensitivity, reduction of visceral and subcutaneous fat, and an equivalent postprandial peak of GLP1 [81].

However, there are no ongoing human studies as the owner company is currently working on capitalization. Nevertheless, the rationale and the preliminary physiology results are fascinating. If further clinical studies confirm the rationale, the Sleeveballoon might become one of the first EBTs to target both the stomach and the small bowel.

Gastric Mucosal Devitalization (GMD)

The endoscopist should ablate the gastric mucosa using the standard Argon Plasma Coagulation (APC) to perform the GMD. This procedure's rationale is based on the role of gastric signaling in controlling hunger and satiety, which seems critical after the surgical sleeve gastrectomy [82]. Some experts initially hypothesized that ablating around 70% of the gastric mucosal surface would trigger weight loss. Further animal studies confirmed that the GMD could promote a reduction in body weight, adiposity, and hepatic steatosis. Furthermore, it could ameliorate lipid metabolism, blood pressure, renin, and cardiovascular lipid deposition in rat models [83, 84].

More recently, Kumbhari et al. developed a porcine model comparing GMD, sleeve gastrectomy, and a sham operation. All procedures were technically successful with no adverse events. The endoscopic procedure elicited a more pronounced weight loss at 4 and 8 weeks compared to sham. Weight loss was similar between GMD and SG at 4 weeks, but SG pigs presented a more significant loss at 8 weeks ($p < 0.05$).

These studies suggest GMD might be temporarily effective with few related adverse events. Nonetheless, it seems

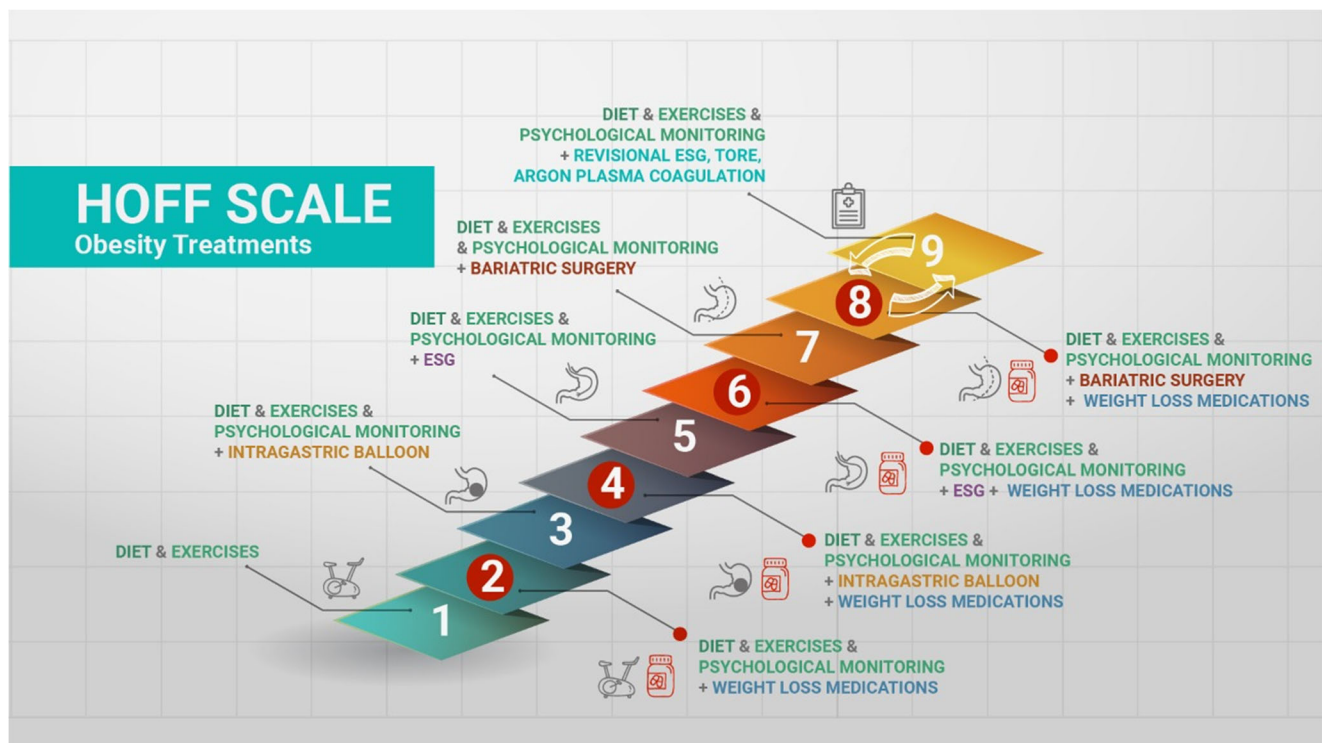


Figure 1 A proposed step-up therapeutic approach for obesity combining all available therapies. ESG, endoscopic sleeve gastroplasty; TORE, transoral outlet reduction. Courtesy of Dr. Ana Carolina Hoff.

repeatable, which could mitigate its transitory trait. Human studies are probably the next step needed to transform GMD into another therapeutic option for obesity.

Magnetic Anastomosis System (GI Windows Inc.)

The endoscopic magnetic partial jejunal diversion (EMPJD) employs self-assembling magnets initially developed to address gastric outlet obstruction [85]. Two magnets should be deployed: the first in the proximal jejunum by upper endoscopy and the other in the terminal ileum by a deep colonoscopy. After deployment, each of them assembles in a ring-shaped octagon as they couple across the intestinal wall in the antimesenteric border. The magnetic force leads to local ischemic and subsequent necrosis. After 2 weeks, the magnets detach from the wall as the tissue mortifies and are naturally expelled during defecation. The result is a calibrated side-to-side jejunoileal anastomosis. This procedure diverges from the abandoned traditional surgical jejunoileal bypass once the original intestinal pathway remains intact. Accordingly, only a portion of food bypasses the small bowel, mitigating the risk for excessive malabsorption.

Ryou et al. published the animal proof-of-concept study in 2016 [86], and soon after, survival models demonstrated that the procedure was safe [87]. The first-in-man study was conducted in the Czech Republic and included 11 patients. Technical success was 83% (10/12—as one patient required

two attempts). However, all but two deliveries required laparoscopic assistance, which was per protocol after 40 min attempting fully endoscopic coupling. Patients presented a gradual progressive weight loss throughout follow-up: mean %TBWL of 8.2%, 10.6%, and 14.6% at 3, 6, and 12 months, respectively. Interestingly, diabetic patients experienced a reduction by 1.9% in HbA1c levels at 12 months. There were no device-related SAEs, and all minor AEs were managed non-operatively [88].

A currently ongoing study (NCT03130244) confirmed that the fully endoscopic coupling is extremely challenging despite the operator's experience. Therefore, the proposed technique has been modified to laparoscopic-assisted. Further studies are needed to establish the effectiveness of the EMPJD in the long term and demonstrate the combined endoscopic-surgical approach's technical viability.

Ideas and Insights for the Future

Obesity is a chronic relapsing disease. As such, several therapeutic options are therefore necessary during its natural history and considering all its grades and particularities. A personalized step-up approach seeking enhanced and sustained results is highly appropriate in this setting. Lifestyle interventions, diet modification, psychological treatment, pharmacotherapy, EBTs, and bariatric surgery are not mutually

excluding. On the contrary, they must act in harmony, recognizing the seriousness of the disease. Endoscopic bariatric procedures may be consistently associated with pharmacotherapy (GLP-1 analogues, for instance), to enhance effectiveness and durability of the results [49••]. Figure 1 represents a proposal for step-up treatment of obesity, known as “the Hoff scale”.

As to the future of endobariatrics alone, more effective procedures will probably address two or three different GI tract targets. To date, some scattered articles have already demonstrated such a trend. Shah et al. performed same-session ESG and transoral incisionless fundoplication in a patient with obesity and gastroesophageal reflux disease [89]. Sawas et al. reported a simultaneous laparoscopic hiatus hernia repair and fundoplication, followed by ESG [90]. Ghaz et al. described sequential duodenal liner and IGB in porcine models [91], while Sartoretto et al. reported a series of 3 individuals receiving concurrent IGB after reaching weight loss plateau with the duodenal liner [92].

Conclusion

Endobariatrics is an ever-growing field with endless evolving possibilities. As such, it will certainly play an essential role in any of the possible future scenarios of the war against obesity.

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- Of major importance

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