

REVIEWS

## Endoscopic treatments of obesity and metabolic disease: Are we there yet?

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*“If one can imagine it, one can create it.”*  
N.S. Navarro Jr.

### ABSTRACT

Obesity and metabolic diseases represent a major problem for our society. For this reason, a number of medical, behavioral, hygienic-dietetic and surgical therapies have been used in an attempt to solve or palliate this problem. In these last years, we have seen a growing number of endoscopic therapies directly targeted to treat obesity and its complications, and its clinical usefulness is relatively unknown. The current review attempts to update what is known on the different endoscopic therapies for obesity, paying special attention to technical aspects and the existing evidence of their usefulness in clinical practice.

**Key words:** Obesity. Endoscopy. Therapy.

### OBESITY PROBLEM

Obesity has reached pandemic proportions. According to the World Health Organization 2010 global burden of disease study, compared to 1990, obesity and its associated conditions are now among the highest contributors to the global burden of disease and have replaced communicable diseases in children as major contributors to this burden (1,2). Mirroring this rise in obesity prevalence is a rise

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in its associated co-morbid conditions including diabetes, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) (3). Indeed, the prevalence of diabetes has grown more than 50 % in the last 3 decades and NAFLD is thought to afflict about 70 % and 50 % of obese adults and children, respectively (4). Of those, about 5 % will progress to cirrhosis and end stage liver disease (5).

Obesity is complex and difficult to address. Its causes are multi-factorial that to address all the issues regarding a high caloric fast-food type diet, sedentary lifestyle, easy availability of modern processed foods, unavailability of fresh healthy food and genetics can be too daunting. The problem is compounded by the fact that most obese patients have associated endocrine, cardiac and pulmonary problems limiting their exercise ability (6).

Lifestyle modification and current pharmacological approaches for the treatment of obesity are generally associated with modest (average 5 kg) weight loss that is poorly sustained in a majority of patients (7). The reasons for this are multifactorial, and include the redundancy of pathways regulating energy intake and expenditure and the counterproductive response to weight loss that often leads to increase hunger and decrease energy expenditure, resulting in regain of the lost weight (8).

Bariatric surgery remains the most effective treatment option for obese patients. Available procedures include laparoscopic and open Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, adjustable gastric band, vertical banded gastroplasty, duodenal switch, and biliopancreatic diversion. RYGB is currently the bariatric surgical procedure of choice. In a meta-analysis of 164 studies including 161,756 patients, RYGB resulted in an average excess body weight loss of 67.5 % at one year, with remission of diabetes in 94 %, of hypertension in 80 %, and of obstructive sleep apnea in 95 %, and dyslipidemia remission in 72 % (9,10). Unlike medications and life-style modifications, the effects

of bariatric surgery seem to be sustained in the long term. Thus, the recently updated Swedish Obese Subjects Study demonstrated mean changes in body weight after bariatric surgery (13 % RYGB, 19 % gastric banding, and 68 % vertical banded gastroplasty) at 2, 10, 15 and 20 years of -23 %, -17 %, -16 %, and -18 %, respectively (11).

Despite proven efficacy, it is estimated that less than 1 % of obese subjects who qualify for bariatric surgery will undergo such intervention (12). This mismatch is fueled by high surgical costs, and morbidity and mortality associated with surgical interventions. Whereas, mortality from bariatric surgery has dropped significantly and is comparable to that of cholecystectomy or appendectomy in bariatric centers with high surgical volumes, early and late complications associated with bariatric surgery continue to be problematic at 17 % and a hurdle for their wide-spread use (10). Early complications include anastomotic leaks, internal hernias, thromboembolic events, bowel obstruction, gastrointestinal hemorrhage, and wound complications. Late complications include gallstones formation, marginal ulceration, anastomotic stenosis, incisional hernia, gastrogastric fistula, and dumping syndrome.

Our understanding of the mechanisms by which bariatric surgery works has evolved from that of mechanical restriction and malabsorption, to that of anatomical surgical manipulations resulting in physiological alterations in gut neuroendocrine signaling, gastrointestinal motility, autonomic nervous system signaling, bile acid production and absorption, and gut microbiota resulting in weight loss and diabetes resolution. Emerging endoscopic technologies have opened the door to using endoscopic approaches and devices to reproduce many of the anatomical alterations of bariatric surgery endoscopically and thereby contribute to the effective treatment of obesity and its associated conditions (13). Early results are encouraging and suggest that endoscopy-based intraluminal therapies may provide the next major treatment advance in this area by providing a cost-effective and minimally invasive alternative to traditional bariatric surgery to allow its application to a wider segment of the obese or overweight population, vulnerable populations such as children and adolescents, and at risk super-obese individuals. This review will focus on endoscopic approaches for the treatment of obesity that are in clinical practice or advanced stages of development and regulatory approval. In discussing these approaches, it is helpful to separate them into gastric and small bowel endoscopic interventions.

## GASTRIC INTERVENTIONS

Gastric volume reduction, whether through the creation of a gastric pouch as in the case of RYGB or gastric sleeve as in the case of sleeve gastrectomy, is important for the success of bariatric procedures. Indeed, recent randomized studies have shown similar efficacy of sleeve gas-

trectomy, a surgical procedure with its sole intervention focused on reducing the gastric volume by 75 to 80 %, compared to RYGB that involve multiple surgical alterations to the stomach and small intestines (14). Both procedures resulted in similar changes in the gut neurohormonal milieu (15). To that end, multiple endoscopic interventions have focused on reducing or restricting the gastric volume as treatment for obesity.

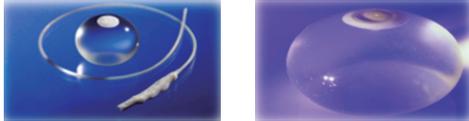
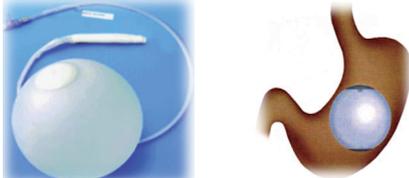
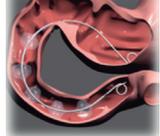
## Intragastric balloon and other space-occupying devices

Endoscopically placed intragastric balloons (IGB) for the treatment of obesity were first introduced to the US market in the mid 80s with the Garren-Edwards Gastric Bubble (GEGB). The GEGB had multiple complications, mainly small bowel obstruction due to balloon deflation requiring endoscopic or surgical retrieval, and it failed to demonstrate efficacy in a prospective, double-blind, sham operated, randomized trial of 59 obese patients with 9 months follow-up period (16). Subsequently, newer generation IGB balloons were developed with the introduction of the BioEnterics Intragastric Balloon (BIB) (Allergan, Irvine, CA) in the early 90s, and the Heliosphere balloon (Heliosphere BAG) (Helioscope, France) in 2004. The BIB is an elastic spherical balloon made from silicone, filled with about 500 ml of saline, and does not require endoscopic placement; whereas, the Heliosphere is a double-bagged polymer balloon covered with silicone, and filled with about 650 to 750 ml of air. Newer IGBs with more sophisticated migration-hindering and deployment/retrieval mechanisms, which also allow for endoscopic balloon volume adjustments, are now available (Table I). IGB may serve as a primary weight loss procedure or as a "bridge therapy" prior to bariatric surgery to decrease the perioperative surgical risk. Currently available IGBs are generally designed to remain within the stomach for up to 6 months prior to their removal.

Several small prospective randomized trials with mid-term follow-up reported the safety and efficacy of BIB for weight reduction (17-20), improvement of metabolic syndrome (17), and non-alcoholic steatohepatitis (NASH) (21). When compared to sham (20), pharmacotherapy (18), and one or two balloons insertion in sequence (19) about 10 % of body weight loss appears to be maintained at 6-12 months after balloon removal. Nausea, abdominal pain, acid reflux, and vomiting are common complaints after IGB placement; however, the majority of these symptoms seem to improve with time and medical therapy without necessitating early balloon removal.

Larger retrospective studies of BIB show about 32 % excess weight loss (EWL) at balloon removal (22). Retrospective studies with longer follow-up, however, have shown maintenance of significant weight loss in only quarter of patients (23). This suggests that long term weight

**Table I. Intra-gastric balloon and other space-occupying devices for the endoscopic treatment of obesity**

<p><b>Sentinel Group</b> Full Sense Device</p>		<p>Induce satiety and fullness in the absence of food by placing pressure on the distal esophagus and cardia of the stomach</p>
<p><b>BioEnteric</b> Intra-gastric Balloon</p>		<p>Elastic spherical balloon made from silicone and filled with about 500 ml of saline</p>
<p><b>Helioscope</b> Heliosphere BAG</p>		<p>Double-bagged polymer balloon covered with silicone, and filled with about 650 to 750 ml of air</p>
<p><b>Spatz</b> Adjustable Balloon System</p>		<p>Saline filled IGB with an attached migration-hindering catheter, and an extractable inflation tube for volume adjustment, while the IGB remains in the stomach</p>
<p><b>Bioflex</b> Adjustable Balloon System</p>		<p>Air filled IGB that is delivered over a Savary guide-wire with a valve that connects and disconnects to the delivery and volume adjustment systems with a screw-like mechanism</p>
<p><b>Silimed</b> Intra-gastric Balloon</p>		<p>Saline and 2 % methylene blue filled IGB that is delivered to the gastric fundus with and endoscopic snare</p>
<p><b>Endball</b> Endalis</p>		<p>Air filled intra-gastric balloon with over the scope delivery system allowing for delivery under direct visualization</p>
<p><b>ReShape</b> Dual-Balloon ReShape Medical</p>		<p>Endoscopically inserted, saline filled, dual intra-gastric balloon system with the two balloons attached to each other by a flexible tube. Each balloon has independent channels so that unintentional leaks or deflation in one balloon are designed not to impact the other balloon</p>
<p><b>SatiSphere</b> Endosphere</p>		<p>Endoluminal mechanical device implanted endoscopically and composed of nitinol backbone and spheres made of polyethylenterephthalat with two pigtails ends</p>

loss maintenance with IGB is difficult to achieve. Since significant perioperative weight loss improves surgical risk, IGB may well be suited as an effective bridge rather than primary treatment for obesity.

Ponce and colleagues evaluated the safety and efficacy of double-balloon placement, ReShape Medical (San Clemente, CA) (24). The two balloons are interconnected and filled with 900 ml saline (450 ml each balloon). The perceived advantage of the double balloon design is that it can occupy more gastric luminal space and if one balloon deflates the other remains intact preventing migration. In a study of 30 patients in Europe, 21 randomized to the double-balloon therapy, the mean %EWL at 24 weeks (balloon removal) was 31.8 % compared to 18.3 % in the control group. At 48 weeks, 24 weeks after device removal, the balloon group maintained 64 % of their weight loss. No deaths, unanticipated adverse effects, early removals, balloon deflations, or balloon migrations occurred (24).

Other non-endoscopically placed balloons or space occupying devices are also available. The Ullorex Balloon (Phagia Technologies, Inc. USA) is a large capsule that is filled with citric acid and swallowed without endoscopy. It inflates inside the stomach in 4 minutes. The gastric acid degrades a plug in the balloon after 30 days, which will cause it to deflate and get excreted in the feces. A pill the BaroNova (BaroNova therapeutics Inc. Foster City, CA) also expands inside the stomach for a week and then degrades (25).

Additional space-occupying devices for the treatment of obesity are at different stages of development. The TransPyloric Shuttle (TPS, BAROnova Inc.) device is an endoluminally delivered funnel type device that delays gastric emptying by intermittent sealing of pylorus with peristalsis. The SatiSphere (Endosphere Inc. Columbus, OH) is an endoluminal mechanical device implanted endoscopically composed of nitinol backbone and spheres made of polyethylene terephthalate with two pigtail ends. It is implanted under general anesthesia and placed into in a C loop configuration extending from the antrum to the duodenum. This device has high migration rates and its future is uncertain. The Full Sense™ (Sentinel Group Inc.) device is a covered metal stent like device placed across the gastroesophageal junction endoscopically and hypothesized to induce satiety and fullness in the absence of food by placing pressure on the distal esophagus and gastric cardia.

## Gastroplasty techniques (Fig. 1)

### TOGA

Transoral gastroplasty, the TOGA system (Satiety Inc, Palo Alto, CA. USA) consisted of a disposable vacuum based stapling device and a second restrictor device. It created a staple line along the lesser curvature of the stomach to mimic a surgical vertical banded gastroplasty that

restrict food intake. It does not remove any portions of the stomach. A multi-center trial involving 67 patients with a 12 month follow up showed an average of 38.7 % EWL at 12 months with significant improvement in diabetes parameters (26). The procedure was well tolerated. Satiety Inc., terminated its operations and sold its assets due to less than satisfactory subsequent outcomes data.

### TERIS

TERIS was a transoral endoscopic restrictive system (BaroSense, Redwood, CA. USA) that endoscopically places a restrictive silicone device with a 10 mm orifice anchored by five silicone anchors through five transmural plications at the gastric side of the gastroesophageal junction to replicate the effects of a laparoscopic gastric band. De Jong and colleagues reported their experience in 13 subjects followed for 3 months. The median procedure time was 142 min under general anesthesia. Serious complications were reported in three subjects (two pneumoperitoneum requiring percutaneous intervention, and one gastric perforation). The safety profile of the procedure improved after adjusting the stapling device and performing the procedure with carbon dioxide insufflation. The median reported EWL at 3 months was 28 % (27). This device and company has since been terminated.

### EndoCinch

The EndoCinch was a vacuum based over the scope suturing device (Bard/Davol, Warwick, RI). Fogel and colleagues first described the use of the EndoCinch device for the creation of an endoluminal vertical gastroplasty as a primary treatment for obesity in 64 subjects. This study was a single-center, uncontrolled study with a 1-year follow up. The procedure was performed in roughly 60 min under general anesthesia. The percentage EWL reported was  $58 \pm 19.9\%$  with a favorable safety profile (28). The durability of the tissue plications was not adequately assessed in this study. The TRIM (Transoral gastric volume Reduction as Intervention for weight Management) study used a second generation of the EndoCinch to create a similar gastroplasty in an open-label, prospective, multicenter, single-arm study enrolling 18 patients with one year follow-up (29). The mean excess weight loss at 12 months was  $27.7\% \pm 21.9\%$ ; however, the suture plications were not durable as demonstrated by repeat endoscopy at 12 months.

### Primary Obesity Surgery Endolumenal (POSE) procedure

POSE uses a per-oral incisionless Operating Platform™ (IOP) (USGI Medical, San Clemente, CA. USA) to place transmural tissue anchor plications that reduce gastric fun-

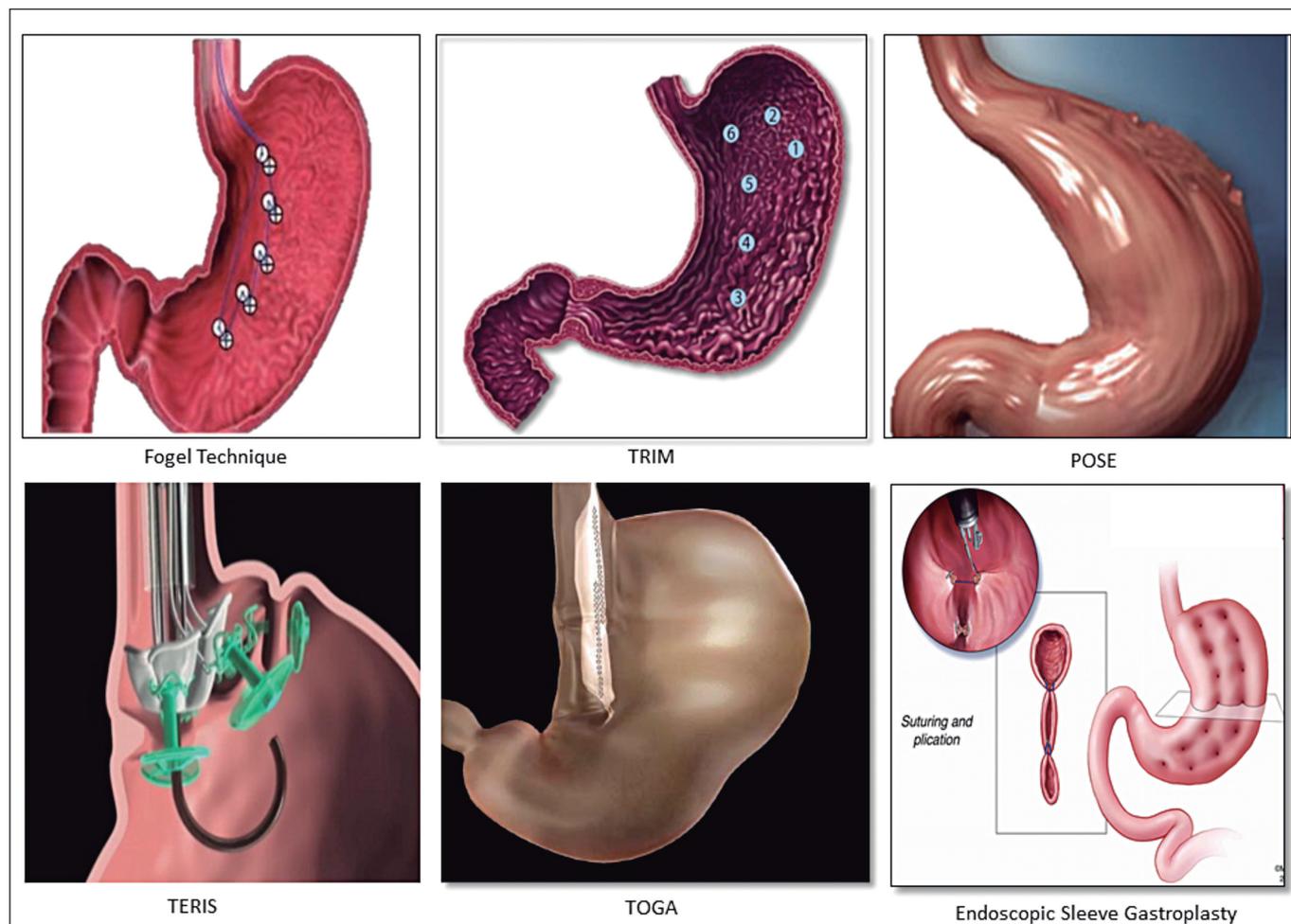


Fig. 1. Endoscopic gastroplasty techniques obesity -TRIM: Transoral gastric volume reduction as intervention for weight management; POSE: Primary obesity surgery endolumenal procedure; TERIS: Transoral endoscopic restrictive system; TOGA system: Transoral gastroplasty; Endoscopic sleeve gastroplasty (Apollo).

duodenum accommodation and parts of the distal gastric body. This large overtube-styled platform has four working channels that can accommodate a slim endoscope and three specialized instruments: The g-Prox EZ® Endoscopic Grasper, a flexible shaft with a jawed gripper for creating and approximating a full thickness (serosa to serosa) tissue fold; the g-Lix™ Tissue Grasper, a flexible probe with a distal helical tip designed to assist the g-Prox in capturing target tissue for a full thickness mini-plication; and the g-Cath EZ™ Suture Anchor Delivery Catheter, a catheter system with a needle at its distal tip that, after advancement through the lumen of the gProx, penetrates the mobilized target tissue and installs a pair of pre-loaded paired tissue anchors joined by suture material holding the plication until there is serosal fusion. Results of a single-center, open-label, prospective trial enrolling 45 obese patient mostly with class I and II obesity demonstrated the feasibility and safety of the technique. A mean of 8.2 suture anchors were placed in the fundus and 3 in the distal body. Mean opera-

tive time was about 69 minutes and all patients were admitted for observation. Patients lost about 13 kg at 6 months representing 49 % EWL. The procedure was well tolerated (30). A large US pivotal, multicenter, randomized, sham-controlled study of this platform is being planned.

### **Endoscopic sleeve gastroplasty**

Using an FDA approved and commercially available improved endoscopic suturing device (Overstitch; Apollo Endosurgery, Austin, Tx. USA), Abu Dayyeh and colleagues demonstrated the feasibility of transoral endoscopic gastric volume reduction in a fashion similar to, but not identical to, sleeve gastrectomy accomplished by a series of endoluminally placed free-hand, full-thickness, closely spaced sutures through the gastric wall from the prepyloric antrum to the gastroesophageal (GE) junction (31). Unlike other endoscopic gastric reduction techniques

for weight management that only replicate the vertical banded gastroplasty or the gastric band without reduction of the antrum or fundus, this technique reduces the entire stomach (Fig. 1). A multicenter trial of this technique is ongoing and early results are encouraging.

### Aspiration therapy (Fig. 2)

Aspiration therapy is a novel treatment approach for obesity that allows obese patients to dispose of a portion of their ingested meal by placing a specially designed gastrostomy tube, known as the A-Tube™ in the stomach. The aspiration procedure is performed about 20 minutes after the entire meal is consumed and takes about 5-10 minutes to complete. The apparatus that enables patients to aspirate is known as the Aspire Assist (Aspire Bariatrics, King of Prussia, PA. USA). This approach provides an effective mean of portion control and has been efficacious in pilot prospective trial. Eighteen subjects were randomized in a 2:1 ratio to 1 year of aspiration therapy (AT) plus lifestyle intervention (BMI =  $42.0 \pm 4.7$  kg/m<sup>2</sup>) or lifestyle intervention alone (LIA) (BMI =  $43.4 \pm 5.3$  kg/m<sup>2</sup>). The AT group were permitted to continue therapy for an additional 1 year (2 years total). Seven of 11 patient randomized to AT opted to continue for 2 years. Ten of 11 AT and 4 of 7 LIA subjects completed the initial 1 year. Among completers, AT and LIA subjects lost  $18.3 \pm 7.6$  % ( $49.0 \pm 24.4$  percent excess weight loss (%EWL)) and  $5.9 \pm 10.0$  % ( $14.9 \pm 24.6$  %EWL) body weight, respectively. The seven subjects who completed 2 years of AT maintained a  $20.1 \pm 9.3$  %

body weight loss ( $54.6 \pm 31.7$  %EWL) at 2 years (32). A pivotal multi-center, randomized, controlled, open-label, 52-week trial to support FDA approval of this device is currently underway in the US.

### SMALL BOWEL INTERVENTIONS

#### EndoBarrier gastrointestinal liner (Fig. 3)

Endoscopic implantation of a duodenal-jejunal bypass sleeve made from a Teflon liner (EndoBarrier, GI Dynamics, Lexington, MA) shows promise and efficacy in the management of obesity and associated diabetes (33,34). When deployed in the duodenal bulb under endoscopic and fluoroscopic guidance, this impermeable fluoropolymer sleeve, extending 60 cm into the small bowel, creates a mechanical barrier that allows food to bypass the duodenum and proximal jejunum, thus potentially manipulating the enteroinsulin system. Several prior studies have documented the technique's feasibility and efficacy on weight loss and improvement in obesity comorbidity especially diabetes and NASH (33-37). This device has a favorable safety profile. A pivotal US multicenter FDA registry trial for this device is currently underway.

#### Gastroduodenojejunal bypass sleeve

The Gastroduodenojejunal bypass sleeve (ValentTx, Inc., Hopkins, MN. USA) is a longer sleeve (120 cm) that

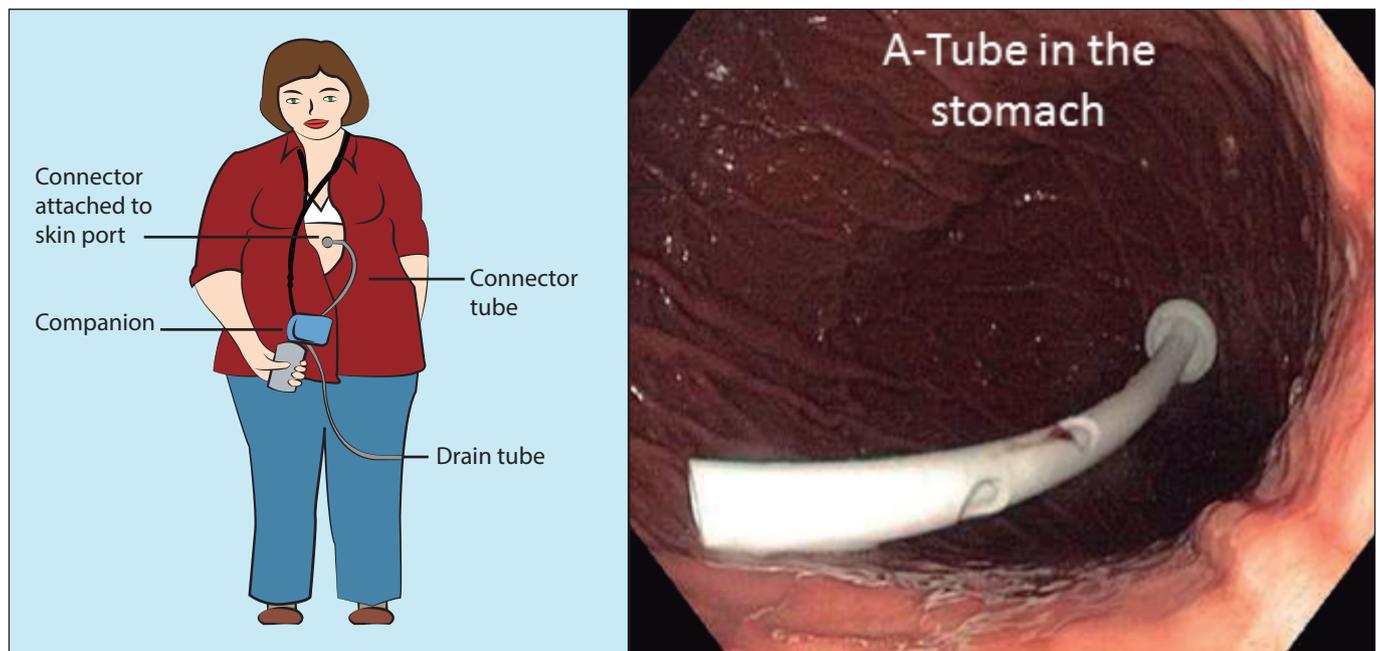


Fig. 2. Aspiration therapy for obesity.

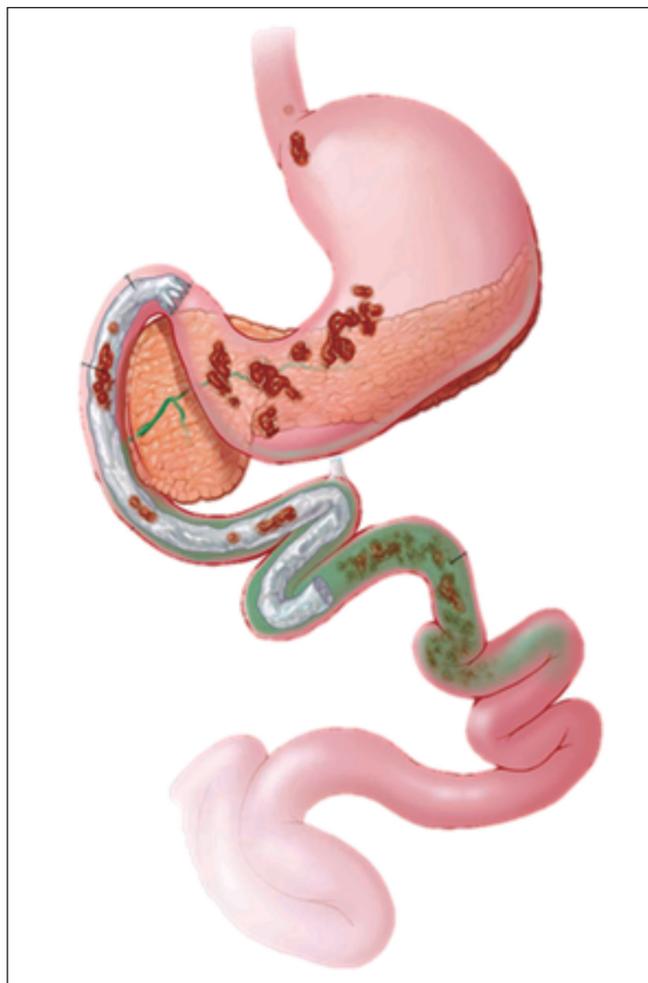


Fig. 3. EndoBarrier® gastrointestinal liner.

is endoscopically and laparoscopically implanted. The sleeve is deployed at the level of the gastroesophageal junction and is anchored laparoscopically. The procedure mimics more the RYGB where the sleeve excludes the stomach, duodenum and proximal jejunum. In a series of 22 patients, the 3 month %EWL was 40 %. Premature device removal occurred in 5 patient (23 %) secondary to odynophagia within the first 3 weeks. It was noted that in their short term experience diabetic patient enrolled in this study had significant improvement in their diabetes resulting in medication discontinuation (38).

## OTHER PROCEDURES

### Gastric pacing/vagal nerve stimulation

Although these procedures are done laparoscopically, potential for endoscopic use is not far from the horizon. Gastric pacing involves placing probes through the sero-

muscular antral area and implanting a subcutaneous pacemaker device to connect to the probes (39). The idea is to provide continuous or pulsating stimulation to the stomach to decrease emptying time, reduce appetite, and enhanced satiety. It may also affect the neuro-hormonal gut brain axis in terms of inducing satiety and reduces pancreatic enzyme secretion that induces malabsorption.

The Mayo Clinic Developmental Endoscopy Unit has applied their original submucosal endoscopic tunneling method, referred as SEMF (submucosal endoscopy with sealant mucosal flap) to explore direct endoscopic implantation of the vagal pacing leads. Access to the vagal trunks is achievable; however, the technique for actual deployment of the entire nerve stimulation system has yet to be developed. The Mayo team in the late 1980s demonstrated endoscopic vagotomy to be possible using laser transmural laser ablation but abandoned the method due to high complication rates. The SEMF procedure could alternatively be used to destroy a vagal trunk as an adjunct treatment for obesity.

## NOTES

The field of hybrid natural orifice transluminal endoscopic surgery (NOTES) shows promise in reproducing different components of bariatric surgical procedures endoscopically. Itoi and colleague created EUS (endoscopic ultrasound) guided gastrojejunostomy in 5 pigs (40). This was primarily intended to bypass obstructing pancreatic/gastric lesions, but can be translated to obesity treatment by creating a gastrojejunostomy to bypass the duodenum/pancreas and close the pyloric channel by some endoscopic means which would provide reasonable long term closure. Experimental studies on endoscopically inserted magnets to create gastrojejunostomies or gastroileostomies to induce an ileal break phenomena or even gastrocolic fistulas for the treatment of obesity are also underway (41).

## CONCLUSION

Most of the endoscopic procedures and techniques presented in this review are promising. The lingering question that is yet to be answered is their durability compared to their surgical counterparts. However, despite the clear efficacy of bariatric surgery, we don't believe it will be a feasible solution to address the large number of eligible patients with obesity and metabolic disease. We believe that endoscopic treatments will provide the next major breakthrough in the treatment of obesity by ushering the development of a spectrum of new endoscopic therapies that replicate the physiological benefits of bariatric surgery endoscopically in a cost-effective and minimally invasive fashion. This will enable clinicians to make meaningful strides in the treatment of this epidemic.

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