Endoscopic Treatment of Obesity

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Abbreviations

RYGB	Roux-en-Y gastric bypass
BMI	Body mass index
BPD	Biliopancreatic diversion
GJ	Gastrojejunostomy
EBT	Endoscopic bariatric therapy
IGB	Intragastric balloon
DJBL	Duodenal jejunal bypass liner

Introduction

Obesity increases morbidity and mortality and adversely affects every organ system [1–3]. Recent data suggest that there is a 2–3 fold increase for incremental health care costs in obese adults in the USA compared with normal weight adults [4]. The age adjusted prevalence of obesity in the USA from the 2011–2012 national health and nutrition examination survey (NHANES) was 34.9%, and overall there has been no change in prevalence since the 2003–2004 NHANES [5]. Although it is encouraging that the prevalence of obesity has plateaued in the USA, the lack of a reduction in prevalence highlights the need for additional treatment strategies. With new advances in the development of endoscopic therapy for obesity, endoscopists are poised to fill the gap in current treatment options. This chapter focuses on therapies for endoscopic revision of RYGB and primary endoscopic bariatric therapies.

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Endoscopic Revision of Bariatric Surgery

Weight regain is a significant problem following bariatric surgical procedures. Data from the Swedish obesity study found that after a maximal total weight loss of 38 ± 7 % 1 year after RYGB, only 25 ± 11 % weight loss was maintained at 10 years with 8.8 % of patients maintaining < 5 % total weight loss [6]. This was similar to the findings in LAGB (Laparoscopic Adjustable Gastric Banding) with 21 ± 10 % weight loss at 1 year, 13.2 ± 13 % weight loss at 10 years with 25 % of patients maintaining < 5 % weight loss at 10 years [6]. Christou et al. found a significant increase in body mass index (BMI) from nadir (28.6 ± 0.3 kg/m^2) to follow-up 11.4 years later (33.6 ± 1.3 kg/m^2) [7]. This was most pronounced in patients with a BMI ≥ 50 kg/m^2, with a nadir of 31.4 ± 0.7 kg/m^2 to 38.3 kg/m^2 at follow-up. Further, they used the Reinhold classification (a classification of weight-loss failure after bariatric surgery based on the start BMI) [8] to evaluate 10-year outcomes for RYGB and compared them to previously published data on biliopancreatic diversion (BPD) [7, 9]. They found equivalent rates of weight-loss failure at ≥ 10-year follow-up: patients with a presurgery BMI of < 50 kg/m^2 had follow-up failure rates of 20.2 % and 20.4 % for BPD and RYGB, respectively and patients with a presurgery BMI of > 50 kg/m^2 had follow-up failure rates of 40.9 % and 34.9 % for BPD and RYGB, respectively. Similar findings at 5-year follow-up were also seen by Magro et al. with weight regain seen in 50 % of patients, and higher rates of failure in patients with a presurgery BMI > 50 kg/m^2 [10].

The mechanisms for weight regain are likely multifactorial, but not well understood. Disordered eating behaviors [11–16] and dilated gastrojejunostomy (GJ) diameter and gastric pouch volume [17, 18] correlate with weight regain, but do not account for all weight regain. Obese patients who have undergone RYGB experience a decrease in the hedonic response (how much a stimulus is liked or disliked) to sweet or highly palatable foods [19, 20], and also make healthier food choices [21]. It was also recently shown that at 4–6 months after RYGB with 20 % weight loss, repetitive tasting of sucrose changed from pleasant to unpleasant compared to both baseline testing and to patients who had 20 % weight loss in 4–6 months after laparoscopic adjustable gastric banding [22]. In addition, the RYGB was associated with improvement in eating behaviors [22] and a remission of food addiction in 93 % of subjects with presurgery food addiction [23]. Conversely, weight regain after RYGB has been shown to correlate with the loss of aversion to sweet snacks [24], binge eating, loss of control eating, and grazing behaviors [11–16]. Unfortunately, preoperative food preferences and eating behaviors do not predict weight regain after RYGB. A meta-analysis including five studies of RYGB and five studies of laparoscopic adjustable gastric banding showed no difference in weight loss between binge eating and nonbinge eating groups as assessed prior to surgery [25]. Interestingly, cognitive restraint of eating as assessed by the three factor eating questionnaire improved after revision of the GJ with endoscopic transoral outlet reduction (TOR) procedure in patients who had regained weight after RYGB, and there was a trend toward improvement in uncontrolled eating [26]. These data

suggest that changes to gastrointestinal anatomy affect eating behaviors and food preferences. Moreover, revising the postsurgical anatomy may restore that effect in patients who have regained weight after RYGB.

Both gastric pouch size and GJ diameter have been shown to correlate with weight regain after RYGB. Roberts et al. found a small, but significant correlation between pouch size and weight loss after RYGB at 12 months (R squared = 0.188, $p = < 0.002$) [27]. Campos et al. also found pouch size to be associated with poor weight loss in univariate and multivariate analyses [28]. Heneghan et al. found a significant difference in stoma and pouch size in bariatric surgery patients with weight regain compared with a control group of bariatric surgery patients without weight regain; pouch length 5.0 ± 2.4 cm versus 5.8 ± 2.6 cm, $p = 0.005$ and stoma diameter 2.1 ± 0.8 cm versus 2.5 ± 1.0 cm, $p < 0.001$ in the control compared with weight regain group, respectively [18]. Abu Dayyeh et al. found a significant correlation between weight regain and GJ diameter, even when controlled for other factors related to weight regain ($\beta = 0.19$, $p = 0.003$)[17]. These data support dilated gastric pouch size and GJ diameter as important factors contributing to weight regain after gastric bypass.

Treatment of patients with weight regain after bariatric surgery has been a challenge. Although weight loss has been demonstrated with surgical revision of the GJ and gastric pouch, the complication rates are higher than with the initial procedure [29–32]. This has prompted the evaluation of endoscopic approaches to revise the dilated postsurgical anatomy including suturing, tissue plication, sclerotherapy, and clips.

Endoscopic Suturing

Endoscopic suturing has emerged as an effective tool for GJ and gastric pouch revision. The transoral outlet reduction (TORe) [33–36] procedure was piloted by Thompson et al. in 2006 with the endocinch suturing system (C.R. BARD Inc, Murray Hill, NJ, USA), a superficial suturing device. The technique usually includes mucosal ablation using cautery or argon plasma coagulation, then placing sutures around the dilated stoma to reduce the diameter of the stoma. In practice, additional sutures can be placed in the gastric pouch, if the gastric pouch is also dilated; however, this has not been routinely done in all cases. TORe was demonstrated to produce weight loss or weight stabilization in patients who regained weight after RYGB in a multicenter, randomized sham controlled trial in 77 subjects (active $n = 50$, sham $n = 27$, RESTORe Trial) [35]. The mean procedure time was 107 ± 183 min; and technical success, defined as reducing the GJ to 10 mm or less, was achieved in 89.6% of the subjects. The percentage weight loss in the intention to treat group with the last observation carried forward was 3.5% (95% CI,1.8–5.3%) and 0.4% (95% CI, −2.3 to 3.0%) in the TORe and Sham groups, respectively ($p = 0.021$). More importantly, weight loss or weight stabilization occurred in 96% of TORe patients, but only 78% of controls, $p = 0.019$. A recently published

retrospective analysis of 25 consecutive patients who underwent the TORe procedure with a full thickness suturing device, the overstitch endoscopic suturing system (Apollo endosurgery, Austin, Tx) found that 16 patients who were observed at 12 months lost 56% of the weight that they had regained from their lowest weight after RYGB. More importantly none of those patients continued to gain weight after the TORe procedure while two patients who were known to have a failure of the TORe sutures due to postprocedure vomiting continued to gain weight [37]. Furthermore, in a matched cohort study of superficial thickness suturing devices compared with full thickness suturing devices for TORe, the weight loss with full thickness TORe was superior to superficial thickness TORe (1 year percentage excess weight loss 18.9±5.4% and 9.1±2.3% for full thickness and superficial thickness TORe, respectively)[38]. Adverse events with TORe have included nausea and vomiting, a small gastric mucosal tear with minor bleeding, pharyngolaryngeal pain, bleeding requiring transfusion and constipation. These efficacy and safety data support TORe as a valid approach for GJ and gastric pouch revision for weight regain after RYGB.

Tissue Plication

The incisionless operating platform (IOP) (USGI Medical, San Clemente, California, USA) is a tissue plication system that allows the placement of full thickness tissue anchors, in a procedure called the revision obesity surgery endoscopic (ROSE) procedure. The operating platform, called the TransPort, contains four large working channels which allow the placement of an ultra-slim endoscope and endosurgical instruments. Tissue is grasped and pulled into a tissue approximator. Placing a needle and tissue anchor through this tented tissue creates a full thickness tissue fold. Two small pilot studies in patients with weight regain after RYGB demonstrated short-term weight loss of 7.8–8.8 kg at 3 months after placement of tissue anchors for both GJ diameter reduction and gastric poch volume reduction [39, 40]. Data from a multicenter registry of 116 patients reported 6.5±6.5 kg weight loss at 6 months with stoma diameter reduced by 50% to 11.5 mm, and pouch length reduced by 44% to 3.3 cm [41]. Twelve-month follow-up was available in 73 of those subjects, demonstrating 5.9±1.1 kg weight loss [42]. This device is currently not being offered in the USA, but may be reintroduced in the future.

The StomaphyX device (EndoGastric Solutions Inc, Redmond, Washington, USA) is also a tissue plication device that tents tissue with a suction device and deploys polypropylene H-fasteners to approximate serosal surfaces. This device was first used to treat weight regain in small studies with short follow-up [43, 44]. In one study, 12-month excess body weight loss was 19.5%, but was only reported in six of 39 subjects[43]. A subsequent study of 59 patients with a mean follow-up of 41 months demonstrated a weight loss of 1.7±9.7 kg, and endoscopy on 12 patients revealed no significant difference in pouch or stoma size at 18 months compared to the baseline [45]. Moreover, a randomized sham controlled trial was closed early

because primary efficacy endpoints of reaching ≥15% excess BMI loss on average and BMI of 35 kg/m^2 or less at 12 months were not achieved at the interim analysis. Only 22.2% of patients reached ≥15% excess BMI loss and BMI <35 kg/m^{2}at month 12. However, a significant difference in excess BMI loss was seen in the active compared with the sham group (7.8%±10.7% and 2.0%±8.5% at 12 months, respectively, $p<0.05$) [46]. Due to the failure of meeting the primary endpoints of this trial, EndoGastric Solutions has abandoned StomaphyX as a tool for endoscopic RYGB revision.

Sclerotherapy

Sclerotherapy involves injecting a sclerosant (usually sodium morrhuate) into multiple points around the GJ. The scar formation results in a decrease in the diameter of the GJ with weight loss or weight stabilization in 72–96.5% of patients at 12–18 months [47–52]. The largest study of this therapy followed 231 consecutive patients with an average of 36% weight regain from nadir who underwent 1–4 sclerotherapy sessions between September 2008 and March 2011. The baseline GJ diameter was 19±5 mm and the mean volume of sodium morrhuate used was 16±5 ml per session. The weight regain stabilized in 76% of all patients included in the analysis at 12 months, but it stabilized in 90% of patients who received two or three sclerotherapy sessions. This indicates a need for repeat sclerotherapy to optimize the effect on GJ diameter reduction. Complications of sclerotherapy included abdominal pain, bleeding, small ulcerations, and transient diastolic blood pressure increases [51].

Clips

Over-the-scope-clips (OTSC, Ovesco, Tubingen, Germany) have been primarily been used in the treatment of fistulas as a complication of bariatric surgery. However, one study reported 94 subjects whose stoma diameter was reduced from 35 to 8 mm with placement of up to two OTSCs placed on the opposite sides of the stoma [53]. The mean BMI decreased from 32.8±1.9 to 27.4±3.8 at 12 months.

Summary

Weight regain after RYGB occurs in a minority of patients after RYGB, but has a significant negative impact on those patients. The mechanisms for weight regain are not well understood. Eating behaviors and dilated gastric pouch and GJ anatomy are likely to play a role in weight regain after RYGB. They may also be related to each other and the evidence suggests that changes in the gut anatomy may cause changes

in eating behavior and food preferences. Multiple techniques for endoscopic revision of the GJ and gastric pouch have been evaluated. Randomized sham controlled trials of superficial suturing or plication devices showed similar total weight loss, although one trial was stopped early due to a failure to meet predefined efficacy endpoints. Full thickness suturing procedures and full thickness plication devices have not undergone randomized sham controlled evaluation; however, the case series and one cohort study comparing superficial thickness to full thickness suturing indicate that full thickness suturing or plication is superior to superficial suturing for maximum weight loss and long-term weight maintenance. Sclerotherapy may be an effective treatment, but frequently requires more than one endoscopic sclerotherapy session for maximum benefit. This may limit the overall effectiveness of sclerotherapy.

Further research in endoscopic therapy of weight regain after bariatric surgery is needed. Heneghan et al. demonstrated statistically different, but clinically similar stoma diameter between patients with weight regain and those maintaining their weight loss. In addition, there has been variability in the pre-endoscopic revision stoma and pouch diameter seen in the RYGB revision studies with one third of patients in the RESTORe trial excluded for a GJ diameter < 20 mm. Although most of the endoscopic RYGB revision cases have resulted in cessation of further weight gain, there was significant variability in weight loss. Additional tools to identify patients who would mostly benefit from endoscopic revision of the post RYGB surgical anatomy and when to intervene would allow clinicians to better allocate resources to those patients.

Primary Endoscopic Bariatric Therapy

Bariatric surgery is currently the most effective treatment for obesity and has been shown to be superior to lifestyle therapy (consisting of diet, exercise, and behavior therapy) [54–56] and pharmacotherapy [57] for weight loss, weight maintenance, and treatment of obesity related diseases [56, 58]. Although there has been some recent controversy over the cost-effectiveness of bariatric surgery [59], the majority of cost–benefit analyses demonstrate a long-term cost-effectiveness of bariatric surgery [60–62]. Minor postoperative complications occur frequently, but serious complications or reoperation occur in 7% or less of postbariatric surgery patients and the mortality rate is low [58, 63]. Despite this, < 1% of people who qualify for bariatric surgery actually get surgery [63]. Multiple factors are likely involved in the percentage of patients opting for bariatric surgery including: fear of surgical risks or unacceptable surgical risk due to comorbidities, unacceptable recovery times, limited access, lack of primary care physician referral, and, unacceptable out-of-pocket expense.

Primary endoscopic bariatric therapy (EBT) overcomes many of the barriers preventing patients from undergoing traditional bariatric surgery. First, primary EBT procedures and devices that are currently in practice or are being evaluated in

trials are associated with lower complication rates and shorter recovery times than the bariatric surgery. Some primary EBTs may only require conscious sedation, so sicker patients who may not be good candidates for surgery may still qualify for endoscopic placement of a device. Primary EBT will also likely be more accessible to patients, because the number of primary EBTs that could be performed per year dwarfs the number of bariatric surgeries that are performed per year due to both the higher number of endoscopists (either gastroenterologists or surgeons) that could perform the procedures and the short procedure time allowing for more procedures per day. Further, most gastroenterologists have a strong referral base, potentially lowering the threshold for primary care referrals, and increasing the number of patients that are referred for primary EBT. Lastly, although primary EBT will likely not be covered by third party payers in the short-term, the cost of the procedures will be low enough to appeal to a large number of self-paying patients. Moreover, as the acceptability of these therapies and the improvements in obesity related comorbidities becomes evident, third party payers may cover these procedures in their policies further reducing the barrier to effective obesity treatment. Multiple devices have been or are currently in the development and testing stages for primary EBT.

Intragastric Balloon

The intragastric balloon (IGB) is a space occupying EBT designed to increase satiation with a meal and thereby decrease food intake resulting in weight loss. Currently, no IGBs are approved for use in the USA, however several balloons have been approved for use around the world. The Garren-Edwards gastric bubble was the first IGB that was approved for use by the FDA in 1985. In 1992, it was taken off of the market due to both safety concerns and lack of efficacy. The device had a cylindrical shape with edges which damaged the mucosa and was made from polyurethane that was too easily deflated. This led to the mucosal breaks and ulcerations in the stomach as well as deflations which caused small bowel obstruction after the deflated device migrated into the small bowel. Also, there was no difference in weight loss between the device and sham groups in randomized sham-controlled trials [64–71]. The volume of the Garren-Edwards gastric bubble was only 220 ml when fully distended, and evidence suggests that a volume of $\geq$400 ml is needed for a reduction of food intake [72]. Several new designs have been developed which address the issues surrounding the failure of the Garren-Edwards gastric bubble (Table 1). All of the new generation of balloons have spherical shapes and minimize edges that could cause mucosal damage. These devices differ significantly in their designs to mitigate balloon deflation, migration, and small bowel obstruction and to allow fill volumes great enough for weight loss (Table 1). Some of the balloons have features that prevent migration of the device in the event of a deflation including the Reshape Duo balloon (Fig. 1) and the Spatz adjustable balloon. Although all of the balloons listed are designed to be removed endoscopically, some of the balloons may be small enough when deflated to pass through the gastrointestinal tract without causing obstruction.

Table 1 Characteristics of intragastric balloons evaluated in humans

Name	Company	Design	Fill	Placement/ retrieval
ORBERA (formerly Bioenterics Intragastric Balloon)	Apollo endosurgery, Austin, TX	500 ml silicon balloon	500 ml saline with methylene blue	Endoscopic/ endoscopic 6-month duration
ReShape Duo balloon	ReShape Medical, San Clemente, CA	Two 450 ml silicon balloons tethered to a flexible silicone shaft	375–450 ml saline with methylene blue	Endoscopic/ endoscopic 6-month duration
Heliosphere bag	Helioscopie medical implants, Vienne, France	550 cm^3 polyurethane and silicone sphere	550 ml air	Endoscopic/ endoscopic 6-month duration
Spatz adjustable agstric balloon	Spatz FGIA, Jericho, NY	800 ml silicon balloon mounted on a catheter, adjustable after initial placement	500–800 ml saline	Endoscopic/ endoscopic 12-month duration
MedSil balloon	MedSil, Moscow, Russia	700 ml silicon balloon	400–700 ml saline	Endoscopic/ endoscopic 6 months
Silimed gastric balloon	Silimed Industria de Implantes, Rio De Janeiro, Brazil	650 ml silicone balloon	632 ml saline, 20 ml Iopamiron contrast, 10 ml 2% methylene blue	Endoscopic/ endoscopic 6 months
Obalon	Obalon therapeutics, Carlsbad, CA	250 ml balloon, up to 3 placed sequentially	Nitrogen gas	Swallowed pill/ endoscopic 3 months

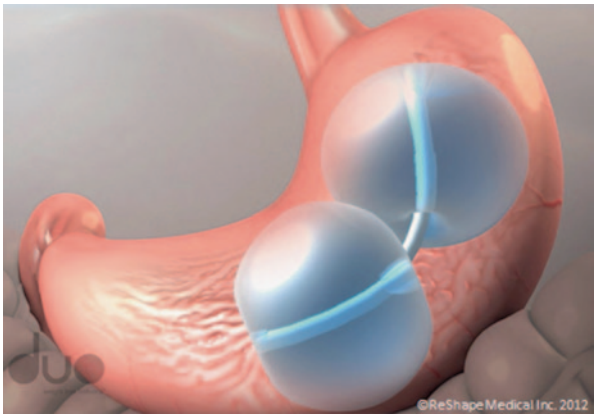

Fig. 1 The ReShape Medical ReShape Duo Balloon inflated in the stomach

IGBs have been shown to be effective at inducing weight loss greater than lifestyle therapy alone or pharmacotherapy alone. A meta-analysis with 3608 subjects demonstrated an estimated mean total body weight loss of 12.2% (14.7 kg) with at least 12 weeks of therapy with the ORBERA balloon [73]. A randomized controlled cross-over trial demonstrated superiority of IGB's to pharmacotherapy. At balloon retrieval (6 months) total weight loss with IGB was 14.5 ± 1.2% compared to 9.1 ± 1.5% in the sibutramine group, $p < 0.05$ [74]. Moreover, at 1 year 50% of patients who received an IGB plus lifestyle therapy maintained ≥ 10% total body weight loss compared to 35% of patients in the sibutraine group.

Long-term weight loss data after one balloon placement is sparse. One studyevaluated patients 60 months after balloon removal; however, only 195/474 patients returned for 60-month evaluation [75]. Total weight loss was 27.3 ± 9.6 kg and 7.26 ± 5.4 kg at the time of the balloon removal and at 60 months, respectively, with 23% maintaining percent excess weight loss > 20%. Although, the maintenance of some weight loss long-term is encouraging, investigators have evaluated the repeated use of IGB for long-term weight loss therapy. Genco et al. reported 100 obese patients who were randomized to receive an IGB for 6 months followed by lifestyle therapy alone or IGB followed by another IGB placement 1 month later for 6 months [76]. Thirteen-month percentage excess weight loss was 51.9 ± 24.6% in the two consecutive IGB group and 25.1 ± 26.2% in the IGB then lifestyle therapy alone group. A subsequent study by Genco et al. followed 83 patients for 6 years, and replaced the IGB after the patients regained ≥ 50% of the weight lost from the previous IGB placement [77]. All patients required a second balloon placement after an average of 12 months (range 1–55 months). Eighteen patients required a third balloon and one patient required a fourth balloon. Initial BMI prior to the first balloon placement was 43.7 kg/m^2, and 37.6 kg/m^2 at 76-month follow-up. However, 18 patients underwent bariatric surgery instead of continuing balloon placement between 12 and 72 months after the first balloon was removed.

The rate of serious complications in a large case series of 2515 patients was < 3% and including gastric perforation, gastric or small bowel obstruction, esophagitis, and gastric ulceration [78]. Two deaths related to gastric perforations occurred. Common mild to moderate adverse reactions in the first few days after balloon placement include nausea, vomiting, and abdominal pain which occur in most patients for the first few days after device placement. This was treated with oral medication and hydration in an outpatient setting in most patients, and typically resolved in a few days.

Taken together, these data suggest that the current generation of IGB has lower complication rates and better efficacy than the first generation of IGB. Although acute postplacement nausea, vomiting, and abdominal discomfort occurs, it is controlled with oral medications and dietary changes in most patients. IGB placement is an effective tool for short-term weight loss, and is superior to both lifestyle therapy alone and pharmacotherapy. Long-term weight loss does occur in some patients after IGB removal, but repeated balloon placement based on weight regain may be a better strategy for long-term weight control. Additional research is needed to address these long-term management questions.

Fig. 2 The GI Dynamics EndoBarrier, a duodenal jejunal bypass liner

Duodenal Jejunal Bypass Liner

The duodenal jejunal bypass liner (DJBL; EndoBarrier, GI Dynamics, Boston, MA; Fig. 2) is an impermeable flouropolymer duodenal jejunal liner that extends 60 cm into the small bowel. The device is placed endoscopically and anchors in the duodenal bulb via a nitinol anchor with barbs that allow for reversible fixation. Ingested nutrients flow into the liner, which prevents contact with the intestinal mucosa or biliary secretions until the liner ends in the mid-jejunum, creating a functional bypass of the duodenum and proximal jejunum which mimics the biliopancreatic limb of a RYGB.

Multiple studies have demonstrated the efficacy of bariatric surgery in treating type 2 diabetes, including two recent randomized control trials of bariatric surgery compared with the intensive medical and lifestyle therapy for the treatment of type 2 diabetes [56, 79]. The RYGB was superior to medical/lifestyle intervention [56, 79] and laparoscopic adjustable gastric banding [56] at inducing partial or complete remission of type 2 diabetes. Animal models suggest that jejunal nutrient sensing after duodenal exclusion plays a role in the early improvement in glycemic control after duodenal jejunal bypass surgery [80], and support the hypothesis that exclusion of the biliopancreatic limb has weight loss independent effects on multiorgan insulin sensitivity and glucose metabolism. However, the human studies are less clear and confounded by the effect of calorie restriction and altered metabolic responses to a meal which occurs immediately after surgery [81–84].

Initial experience with the DJBL demonstrated the device to be superior to lifestyle therapy in multiple short (12–24 weeks) single arm and randomized controlled trials for weight loss [85–87]. Subjects in the DJBL group achieved 19.0–23.6% excess weight loss (EWL) compared to 5.3–6.9% EWL in the control groups. A longer therapy has subsequently been shown to produce more weight loss, and a single arm trial with 52 weeks of therapy in 39 subjects demonstrated 22.1 ± 2.1 kg weight loss (19.9 ± 1.8% total body weight loss) [88]. A sham controlled trial for preoperative weight loss demonstrated lower weight loss 11.9 ± 1.4% compared with 2.7 ± 2% excess weight loss in the DJBL ($n = 13$) and control groups ($n = 24$), respectively ($p < 0.05$) [89]; however, another 24 week randomized sham-controlled trial demonstrated superiority of the DJBL over sham control for decreasing HbA1c in patients with type 2 diabetes (−2.4 ± 0.7% and −0.8 ± 0.4% in the DJBL and control groups, respectively, $p < 0.05$) [90]. Similar decreases in HbA1c were also seen in a single

arm 24-weeks trial (HgbA1c 8.4±0.2% to 7.0±0.2% from baseline to end study, $p<0.01$)[91], but more importantly, glycemic control after a liquid mixed meal test improved 1 week after implantation before any significant weight loss occurred, suggesting that the effect on glucose control may be weight loss independent. Subsequently, longer studies have been performed out to 52 weeks including a study in obese diabetic subjects with a 52-week HbA1c reduction of −2.3±0.3% in 13 subjects [92]; and in subjects with lower BMI (30.0±3.6 kg/m^2) with a week 52 HbA1c reduction from 8.7±0.9% to 7.5±1.6% (baseline to end study, respectively, $p=0.004$) with only 6.5±4.1 kg weight loss [93].

A few serious adverse events have been reported and no deaths have occurred in relation to the DJBL. One duodenal perforation requiring laparoscopic closure has been reported [94]. Of note, 17–40% of subjects enrolled in the studies mentioned above had early device removal predominantly due to complications including: gastrointestinal bleeding, abdominal pain, nausea and vomiting, anchor migration, or obstruction. However, in most of these cases, the issues resolved with the removal of the device.

The efficacy data and relative safety of this device are promising as an effective treatment for obese subjects and potentially even overweight subjects with diabetes. A large multicenter randomized sham controlled trial of this device in diabetic subjects is currently underway in the USA. This will provide crucial information on efficacy and safety end points as well as further information on any persistent effects of the DJBL on glucose control after the device has been removed.

Intragastric Suturing to Alter Gastric Anatomy

A number of different approaches have been studied for per-oral gastric volume reduction. Transoral gastric volume reduction in the TRIM (transoral gastric volume reduction as intervention for weight management) trial utilizing the RESTORe suturing system (Bard/Davol, Warwick, RI) to plicate the anterior and posterior walls of the stomach was first reported in humans in 2010 [95]. This procedure reduces gastric volume by using a plication device to approximate the anterior and posterior gastric walls, and is thought to be a restrictive procedure. A total of 18 patients received an average of six plications; however, only 14 subjects completed 12 months of follow-up demonstrating a weight loss of 11.0±10.0 kg (excess weight loss 27.7±21.9%). No serious adverse events occurred, but plication was only successful in 16 patients and at the 12-month endoscopy, all sutures had spontaneously released in five subjects [95].

Transoral gastric volume reduction has also been reported with the overstitch endoscopic suturing system (Apollo Endosurgery, Austin, Tx; Fig. 3) in a single center pilot study. The full thickness endoscopic suturing device was used to create an endoscopic sleeve gastroplasty in four subjects [96]. The weight loss data are not available; however, a repeat endoscopy at 3 months in two patients revealed intact endoscopic gastric sleeves with only a small portion of the sleeve open in the

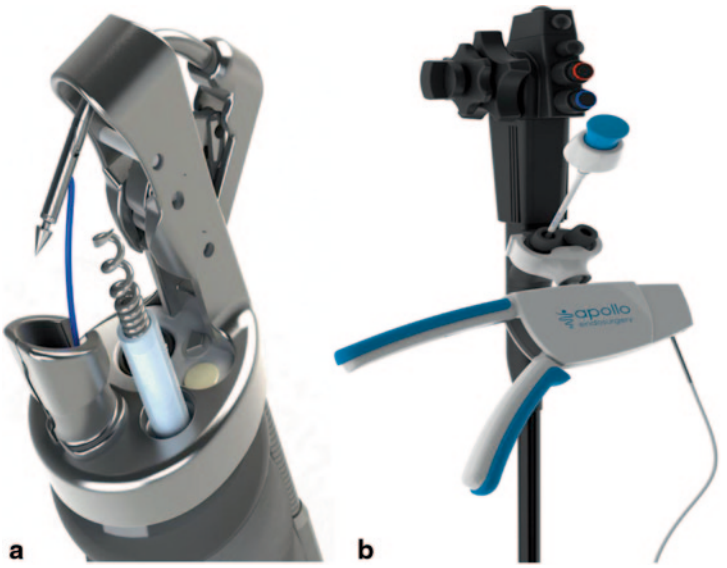

Fig. 3 The Apollo Endosurgery Overstitch tip with suturing arm and tissue helix on the end of an endoscope (panel A) and Apollo Overstitch handle attached to dual lumen endoscope (panel B)

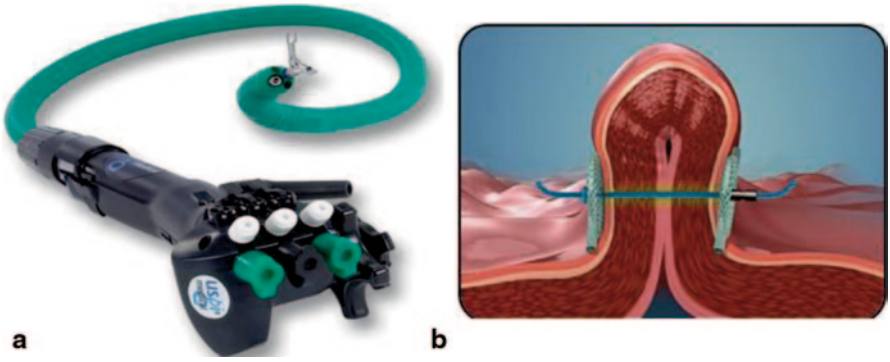

Fig. 4 The USGI Medical IOP Transport (panel A) and tissue plication with suture anchors (panel B)

gastric fundus of one subject. No serious adverse events occurred, but nausea and abdominal pain occurred in three patients, with one patient admitted for conservative therapy. All symptoms resolved by 72 h post-procedure. Since the overstitch endoscopic suturing system has been approved for intragastric suturing by the Food and Drug Administration (FDA), select centers in the USA and abroad have now started offering this therapy.

The IOP (USGI Medical, San Clemente, California, USA, Fig. 4) has also been used to create gastric tissue plications as a primary weight-loss procedure (primary obesity surgery endoluminal, POSE). This procedure involves creating tissue pli-

cations in the fundus and in the distal gastric body, which is thought to impair both gastric accommodation with a meal and delay gastric empyting. This increases satiation with a meal and satiety between meals, reducing food intake to produce weight loss. Results of a single arm, single center study of 45 patients was published in 2013. The 6 month data were only available for 27 of the subjects and demonstrated 16.3 ± 7.1kg (15.5 ± 6.1 %) total weight loss [79]. No serious adverse events occurred. Minor post-operative adverse effects included sore throat, abdominal pain, nausea, and chest pain; however, these typically resolved within 24 h and did not require additional hospital stay. A multicenter randomized sham-control trial is currently underway in the USA to further investigate the effectiveness of this procedure.

Transoral mucosal excision with sutured gastroplasty, which employs the use of both a tissue excision device and suturing device to create a gastric pouch similar to the pouch created with laparoscopic adjustable banding, has been demonstrated to be feasible in four patients [97]. The BMI ranged from 39–61 kg/m2, and percentage excess weight loss ranged from 0–68 % at 24 months. One subject had evidence of perforation on chest x-ray on post-operative day 1; however, no perforation was detected on a combined laparoscopic/endoscopic procedure performed that day. The patient did recover, but an endoscopy performed at 6 months demonstrated a loose gastroplasty with no food restriction.

Although gastric volume reduction is still in its infancy, the initial data is promising as a means to alter gastric anatomy without the need for external incisions. Further studies are necessary to evaluate the efficacy and long-term durability of these procedures.

Aspiration Therapy

Aspiration therapy involves the use AspireAsisst™ system (Aspire Bariatrics, King of Prussia, PA, Fig. 5) to remove up to 30 % of the calories consumed in a meal for weight loss. This is done through a gastrostomy tube called an A-Tube, which is placed with the pull technique commonly used for placement of percutaneous endoscopic gastrostomy tubes. This is capped with a skin port that allows for connection to the companion, which is a hand held device that allows for bidirectional flow of fluid either into the stomach or out of the stomach controlled by an external lever. Patients infuse tap water to aid with aspiration of gastric contents, and then switch the direction of the flow to allow gastric contents to drain out into the toilet. Data from one randomized control pilot study demonstrated superior weight loss in the aspiration therapy group ($n = 10$) compared to the lifestyle therapy only group ($n = 4$) at 1 year (18.6 % ± 2.3 % and 5.9 % ± 5.0 % total body weight loss, respectively; $p = 0.021$). Lifestyle therapy consisted of 15 individual therapy sessions plus quarterly group sessions. 7 out of 10 subjects in the aspiration therapy group completed 2 years of therapy and were successful in maintaining their weight loss; 21.2 % ± 2.8 % total body weight loss at 1 year and 20.1 % ± 3.5 % total body weight

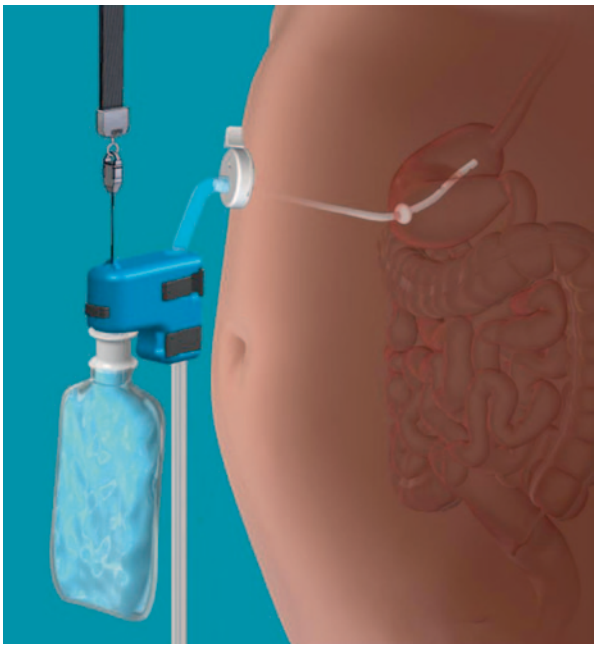

Fig. 5 The components of the Aspire Bariatrics Aspire-Assist™ System assembled for aspiration

loss at year 2, respectively; $p = 0.547$[98]. Multiple psychological evaluations were performed in these subjects, which demonstrated no adverse effects of this therapy on eating behaviors. Indirect measurements of food consumption also suggest that subjects did not eat more to compensate for calories that were aspirate. No serious adverse events occurred; however, abdominal pain in the first 4 weeks after device placement and peristomal skin irritation were common. Pain after the first 4 weeks of device placement was common with the initial A-Tube design used in the study. The A-Tube was modified during the trial to an all-silicone tube. The sustained weight loss and safety profile of the aspiration therapy support further evaluation of this therapy. More recently, preliminary results of a pilot trial conducted in the Czech Republic on six super obese patients (BMI 59.5–71.9 kg/m^2) were presented as an abstract [99]. Weight loss at 3 months was 15.5 kg. Only two subjects had reached the 12-month time point at the time of the abstract, with an average weight loss of 42 kg. Only three minor adverse events occurred, procedure success rate was 100 %, and all subjects were still using the therapy at the time of the abstract presentation. These early results suggest that the aspiration therapy may be a good long-term treatment for obesity even in the super obese population. Further studies are currently underway in Europe for obese and super obese subjects, and in the USA, a multicenter trial is also being conducted in obese subjects.

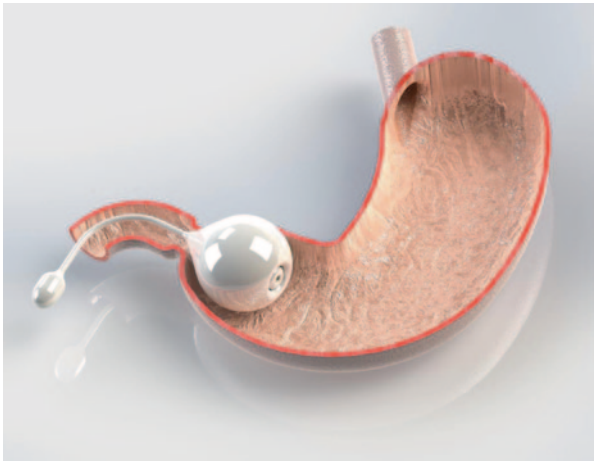

Fig. 6 The BAROnova TransPlyoric Shuttle in the pyloric position

TransPyloric Shuttle

The transpyloric shuttle (TPS, BAROnova Inc., Goleta, CA; Fig. 6) is a spherical bulb that is connected to a smaller spherical bulb by a flexible tether. The larger spherical bulb intermittently obstructs the pylorus, which is thought to delay gastric emptying and promote satiation resulting in early termination of a meal. One pilot trial has been reported in 20 subjects (BMI 36.0 ± 5.4 kg/m^2) [100]. The subjects were divided into two groups; a 3-month cohort ($n = 10$) with the TPS removed at after 3 months and a 6-month cohort ($n = 10$) with the TPS removed after 6 months. Subjects in the 3-months cohort achieved 8.9 ± 5.0 % total body weight loss while the 6 month cohort achieved 14.5 ± 5.8 % total body weight loss. No serious adverse events occurred and the TPS was generally well-tolerated without nausea or abdominal pain even immediately after device placement. However, ten subjects developed gastric ulcerations, and two of those subjects required early device removal (one in the 3-month cohort and one in the 6-month cohort).

Smart Self-Assembling Magnets for Endoscopy

Creation of gastroenteric anastomoses with smart self-assembling magnets for endoscopy has been shown to be technically feasible in an animal model [101]. The procedure described required advancing the gastroscope into the peritoneal space to secure the small bowel for placement of one set of the magnets. It is possible that this technique may be modified to be used in a human model. This presents a potential new mechanism for permanently bypassing the duodenum and proximal jejunum for weight loss and treatment of diabetes without the need for external incisions.

Summary

Primary EBT fills an important gap in the treatment of obesity. Multiple devices currently being studied are poised to meet FDA requirements for approval. While these new technologies provide an important step forward for obesity treatment, they do present new challenges for gastroenterologists. First, these devices and procedures were studied in conjunction with the lifestyle therapy. Endoscopists who wish to use these therapies for their patients will be required to develop an aftercare program that includes weight management program or partner with a reputable bariatric program. Secondly, the EBTs presented in this chapter have different mechanism of actions, and each one likely benefits a subpopulation of obese patients. The endoscopists will need to develop a skill set that allows them to determine which therapy best suits each individual patient based on a variety of patient characteristics. Third, these devices and procedures will likely not be covered by third party payers when they are initially introduced into the market. This will force the endoscopists to explore new financial models currently in place for other self-pay medical services.

Conclusions

Bariatric endoscopy for both weight regain after RYGB and for primary therapy is rapidly progressing into an important part of obesity therapy. A few therapies are already available for endoscopists, and multiple therapies will likely be commercially available in the next few years. While this opens the door to the endoscopists providing important therapies for obesity, it also presents new challenges that endoscopists must face in order to use these therapies successfully.

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