Review Article

Development of Bariatric and Metabolic Endoscopy

Shi-Han Li, Yong-Jun Wang, Shu-Tian Zhang

Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Abstract

Objective: With the evolution of society and changes in human lifestyle, obesity is becoming increasingly prevalent worldwide, and obesity-related comorbidities such as diabetes, hyperlipidemia, hypertension, and coronary heart disease are more common. As a result, new devices and methods for bariatric and metabolic endoscopy are being developed for clinical use, offering new options for patients. This review discussed the progress in bariatric and metabolic endoscopy.

Data Sources: This review was based on data in articles published in the PubMed database up to September 2017, with the following keywords: "obesity", "endoscopy", "weight loss", and "metabolism".

Study Selection: Original articles about various endoscopic methods of weight loss and other reviews of bariatric and metabolic endoscopy were included and analyzed.

Results: The technology of bariatric and metabolic endoscopy has advanced rapidly in recent years. The intragastric balloon (IGB), with its comparatively long period of development, is the most mature and widely used instrument. Multiple new endoscopic devices have been created in recent years, with different targets to achieve weight loss. Despite the proliferation of new devices, the lack of clinical data results in a shortage of clinical experience and instruction in the use of this new equipment.

Conclusions: Bariatric and metabolic endoscopy would help obese people lose weight or prepare for bariatric surgery and hopefully alleviate some of the complications of bariatric procedures. Adequate studies and data are still needed for the new endoscopic devices.

Key words: Endoscopy; Metabolism; Obesity; Weight Loss

Introduction

There are approximately 1.3 billion overweight people and 0.6 billion obese people worldwide, and the number is increasing at an alarming rate. Obesity not only affects one's appearance but also plagues global health. Before the drugs and targeted therapy for obesity that are being used in clinics, bariatric surgery remains the most effective therapeutic option for obese people who cannot lose weight satisfactorily through the exercise and diet. Bariatric surgery cannot only allow patients to quickly achieve and maintain effective weight loss, but also alleviate 80% of the complications caused by obesity.[1] According to a survey, traditional bariatric surgery, including laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric bypass (RYGB), and laparoscopic adjustable gastric banding,[2] is chosen for weight loss by <2% of patient. This is because of patient concerns regarding the potential for irreversible trauma and complications. In contrast, endoscopic bariatric surgery is reversible, safer, and has fewer complications. Endoscopic bariatric surgery has developed rapidly in recent years, offering new options to obese patients.[3]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.221283

Endoscopic Methods

Endoscopic methods for obesity target the stomach directly, mainly by restricting gastric space or altering functional gastric volume, gastric emptying, gastric wall compliance, anastomotic compliance after surgery, or food absorption.[4]

Restricting gastric space or altering functional gastric volume

Endoscopic intragastric balloon

The endoscopic intragastric balloon (IGB) was first proposed by Nieben and Harboe[5] in 1982. The Garren-Edwards

Address for correspondence: Dr. Shu-Tian Zhang, Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University, 95 Yongan Road, Beijing 100050, China
E-Mail: zhangshutian@ccmu.edu.cn

Received: 10-10-2017 **Edited by:** Xin Chen
How to cite this article: Li SH, Wang YJ, Zhang ST. Development of Bariatric and Metabolic Endoscopy. Chin Med J 2018;131:88-94.

and Ballobes IGBs were presented primarily, but many clinical trials had shown that the clinical effects of these two types of IGB are poor and the complication rates are high. Therefore, they were soon discarded.[6,7] The Taylor IGB, which was developed more recently, also failed in clinical use because of the lack of relevant and follow-up clinical data.[8] The Orbera IGB system (Apollo Endosurgery, Inc., Austin, TX, USA) and ReShape intragastric double balloon system (ReShape Medical, Inc., San Clemente, CA, USA) are more commonly used now.

The Orbera IGB was approved by the Food and Drug Administration (FDA) in 2015 for adults with body mass index (BMI) of 30–40 kg/m^2. The balloon is inserted and removed through the endoscope. After insertion, the 400–700 ml of saline and methylene blue is injected into the balloon to expand to a spherical shape to occupy the stomach space, increase satiety, decrease caloric intake, potentially induce neurohormonal effects and changes in motility, and eventually result in weight loss.[9] Methylene blue facilitates early detection of balloon leaks or rupture by urine color. Due to the risk of rupture and intestinal obstruction, however, the balloon may only be placed temporarily and should be removed in 6 months. The ReShape and Orbera balloon systems share similarities, but the ReShape balloon system has two balloons and is more suitable for adult patients with obesity-related complications. ReShape is approved by the FDA for adults with a BMI of 30–40 kg/m^2 and one or more obesity-related comorbidities.[10]

An IGB is more suitable for adults with BMI 30–40 kg/m^2.[11] Morbidly obese patients (BMI >40 kg/m^2) or super-obese patients (BMI >50 kg/m^2) can choose to have an IGB procedure in preparation for bariatric surgery to reduce the surgical risk.[12] Imaz *et al*.[13] reviewed 16 studies involving 3608 patients and concluded that when the balloon was removed, the mean BMI reduction was 5.7 kg/m^2, and the percentage of excess weight loss (%EWL) was 32.1%. Complications of obesity such as type 2 diabetes, hypertension, and hyperlipidemia had been alleviated to some degree. Adverse reactions to the IGB included nausea, vomiting, gastrointestinal perforation, gastrointestinal inflammation, and gastroesophageal reflux. Although the IGB is one of the widely used and relatively safe endoscopic devices, there are some contraindications to its use such as prior gastrointestinal surgery, large hiatal hernia, clotting or bleeding disorders, hepatic cirrhosis, and pregnancy.[10]

Orbera's long-term weight loss and obesity comorbidity effects have been investigated. A study of 500 patients showed that, after 5 years, 195 patients maintained a BMI reduction of 2.5 kg/m^2 and %EWL of 12.97%.[14] Another study showed that the rate of hypertension, diabetes, and hyperlipidemia all decreased after 3 years.[15] However, in a meta-analysis by the ASGE Bariatric Endoscopy Task Force, migration and early removal of the Orbera IGB were reported to be 7.5% and 1.4%, respectively.[16] As for ReShape, a prospective, randomized trial showed that, after 2 years, the group treated with ReShape IGB had a %EWL of 25.1%. Balloon deflation occurred in 6% without migration. Early retrieval for nonulcer intolerance occurred in 9%.[17]

Swallowable intragastric balloon

The traditional endoscopic IGB usually needs to be placed and removed with conscious or unconscious sedation through upper endoscopy (UE). However, these procedures bring cost and risk to the patient, especially in those who are obese.[18] In addition, the discomfort of UE may decrease the general acceptance of the treatment.[19] The swallowable IGB was invented to reduce or even eliminate the need for UE.

There are two main types of swallowable IGB. The first is the Elipse Balloon (Allurion Technologies, Natick, MA, USA). It is a swallowable IGB that does not require UE for deployment and removal. It is a gastric balloon that is folded inside a small capsule attached to a thin catheter.[19,20] It can be easily swallowed with water, and the position of the balloon can be confirmed by abdominal X-ray because of its radiopaque ring. The balloon can be filled with 550 ml distilled water containing potassium sorbate preservative and citric acid. After 4 months, the retained balloon can be emptied through a release valve and naturally excreted through the gastrointestinal tract. A pilot study was conducted in 2016 on a prototype version of the balloon. The study enrolled eight patients, and no serious events occurred.[21] A study by Genco *et al*.[19] in 2017 revealed that all 38 enrolled patients lost weight during treatment, and after 4 months, the mean BMI reduction was 4.2 kg/m^2 and the %EWL was 26%. A significant reduction in major comorbidities related to metabolic syndrome can also be seen. Thirty-seven balloons were naturally excreted in the stool, and one balloon was endoscopically removed because of the patient's nausea, demonstrating the effectiveness and safety of the Elipse balloon.[19] A prospective pilot study enrolling 51 patients showed that the %EWL was 40.84% and BMI reduction was 3.42 kg/m^2 with no serious complications recorded.[22] The common adverse events were nausea, vomiting, acid regurgitation, constipation, and abdominal pain, which were mild and could be accommodated. Undoubtedly, the greatest merit of the Elipse balloon is that there is no need to use UE for insertion, enhancing the acceptance and decreasing the expense. However, because the balloon can be excreted through the gastrointestinal tract or emesis, it still poses a risk for intestinal obstruction.[20]

Another device is the Obalon swallowable IGB system (Obalon Therapeutics Inc., Carlsbad, CA, USA). It also can be placed in the stomach by swallowing rather than endoscopy, and its position can be confirmed by X-ray. The difference is that the Obalon system comprises three gas-filled IGBs with a maximum volume of 250 ml each that are placed sequentially at longer than 14-day intervals. All balloons must be removed endoscopically 6 months after insertion of the first balloon.[23] A pilot feasibility study held in 2013 showed that, in all 17 patients, the BMI reduction was 2.9 kg/m^2 and the %EWL was 36.2% when the 12-week treatment period was finished. No unexpected or serious adverse events occurred; the most common adverse events

were stomach pain or cramping, nausea, and vomiting, which were mild to moderate at most.[24] The Obalon system was also applied to children in a pilot study. In the 16 children who finished the treatment, the %EWL was 20.1%.[25] A randomized sham-controlled trial in 2015 showed that significant weight loss through the Obalon system can be maintained for 12 months.[26] Because the balloons are placed one by one at intervals, physicians and patients can decide how many balloons are ultimately needed according to patient acceptance and weight loss during treatment. Weight loss can also be achieved more gradually. Furthermore, the balloons do not need to be excreted through the digestive tract, decreasing the risk of obstruction. There is, however, a case report describing small bowel obstruction caused by an Obalon balloon that had migrated.[27]

Endoscopic sleeve gastroplasty

Endoscopic sleeve gastroplasty (ESG) was initially proposed by Abu Dayyeh *et al*.[28] The procedure requires the assistance of an endoscopic suture system; gastric volume is largely reduced by stitches in the stomach wall to create more gastric folds. The most commonly used endoscopic suture system is the OverStitch system (Apollo Endosurgery, Inc., Austin, TX, USA) that can create a series of intermittent or continuous stitches in a triangular configuration through the whole gastric wall. In addition, to sustain or further improve the weight-loss effect, ESG surgery can be performed repeatedly as necessary.

A study that enrolled 25 patients and recorded outcomes at 1 year after the procedure showed that the mean BMI loss was 7.3 ± 4.2 kg/m^2, and the mean percentage of total body weight loss (%TBWL) was 18.7 ± 10.7%. There were no major intraprocedural, early, or delayed adverse events. Endoscopic examination and imaging studies showed that the stomach maintained postoperative form at 1 year.[29] A multicenter study of 248 patients with a 24-month follow-up showed the %TBWL was 15.17% at 6 months and 18.6% at 24 months. Five (2%) serious, procedure-related adverse events occurred: two perigastric inflammatory fluid collections (adjacent to the fundus), one self-limited extragastric hemorrhage, one pulmonary embolism 72 h after the procedure, and one pneumoperitoneum/pneumothorax requiring chest tube placement. All five patients recovered fully without surgical intervention.[30] However, it is not a totally reversible operation; the stomach does not return to its original shape by about 6 months after operation because of the tissue adhesion.

Endoluminal vertical gastroplasty

Endoluminal vertical gastroplasty (EVG) uses the endoscopic suture system to apply consecutive stitches that close the gap between the anterior and posterior walls of the stomach to reduce gastric volume. To complete the procedure, five to seven stitches are needed to restrict the gastric space. The greatest difference between ESG and EVG is the stitches: triangle-shaped stitches in ESG that suture three points of the gastric wall together, and straight stitches in EVG that suture two relative points together. A study that enrolled 64 patients showed that, at 1-year follow-up, the patients had a significant BMI reduction of 9.3 kg/m^2, and no patients experienced any serious adverse events.[31] Another 1-year follow-up trial showed that, in the past 6 months, some patients experienced weight gain, and some of the stitches had come undone. It is, therefore, difficult to determine whether EVG can bring long-term and stable effects based on the study.[4]

Transoral gastroplasty

Transoral gastroplasty (TOGA; Satiety Inc., Palo Alto, CA, USA) was first clinically applied by Devière *et al*.[32] in 2008. The TOGA system comprises a sleeve stapler and restrictor that creates a vertical sleeve along the lesser curvature and reduces the outlet space. A single-center study involving 29 patients reported BMI reduction of 6.2 kg/m^2 over 2 years.[33] Familiari *et al*.[34] performed TOGA on 67 patients; 53 patients were available at the 12-month follow-up. The %EWLs were 33.9%, 42.6%, and 44.8% at 3, 6, and 12 months, respectively. The patients' blood glucose and blood lipid levels also fell considerably. The main complications were respiratory insufficiency and asymptomatic pneumoperitoneum that were treated conservatively. Long-term evaluation is still needed before definitive conclusions can be drawn for this procedure.

Primary obesity surgery endolumenal

Primary obesity surgery endolumenal (POSE) uses the incisionless Operating Platform (IOP, USGI Medical, Inc., San Clemente, CA, USA) to perform the procedure. Approximately seven to nine suture anchors are placed in the gastric fundus to decrease fundus volume and limit its accommodation in response to a meal, whereas an additional three to four suture anchors are placed in the distal body of the stomach near the proximal antral inlet to induce antral dysmotility and prolong satiety.[16,35,36]

A study of López-Nava *et al*.[36] involving 147 patients showed that, at 1-year follow-up, 116 patients had a %EWL of 44.9 ± 24.4%. Weight loss was more pronounced in younger patients and in those with a higher initial BMI. Patients tolerated the procedure well with no serious adverse events. Short-term adverse events were mainly limited to minor bleeding at the suture site. Another 6-month follow-up study that enrolled 45 patients showed a reduction in BMI of 5.8 kg/m^2 and a %EWL of 49.4%.[37] A prospective multicenter trial showed that POSE was also effective in reducing a dilated gastrojejunal (GJ) anastomosis and shortening the gastric pouch in patients.[38] POSE needs to be done under general anesthesia and is still under FDA review for approval.

Transoral endoscopic restrictive implant system

Transoral endoscopic restrictive implant system (TERIS) was first performed by Biertho *et al*.[39] in 2010. In this procedure, an endoscopically placed restrictive silicone diaphragm is utilized. The diaphragm has a 10 mm orifice that is anchored with transmural plications in the gastric cardia. It can slow down eating speed and reduce food intake

by forming a narrow lumen from the distal stomach to the gastroesophageal junction in the gastric cardia. In a clinical trial conducted by de Jong *et al*.[40] in 2010, 13 patients were enrolled. The surgery was successful in 12 patients. In one patient, the procedure was aborted after a gastric perforation related to stapler malfunctioning occurred. Patients achieved a median %EWL of 28% after 3 months. Median BMI reduction was 4.2 kg/m^2. In 2016 Verlaan *et al*.[41] published a TERIS trial that achieved an %EWL of 30.1 ± 9.8% at 6-month follow-up of 18 patients, confirming the long-term weight loss of the procedure. However, the anchors remained intact in only 62.5% of the patients. Unfortunately, because of this complication, as well as difficulty using and instability of device, the clinical trial and further development of TERIS did not continue.[2]

Articulating circular endoscopic stapler

The articulating circular endoscopic (ACE) stapling device system (Boston Scientific Corp., Natick, MA, USA) utilizes a stapler that can rotate 360° and articulate into complete flexion or retroflexion. The stapler can create a series of large, full-thickness, transmural plications throughout the stomach, restricting gastric volume.[42] In a prospective, observational, Phase 1 study conducted by Verlaan *et al*.[42] in 2015, 17 patients underwent the procedure. An average of eight staples was placed in the fundus and two in the antrum. The median %EWL was 34.9% and mean BMI reduction was 5.7 kg/m^2. Six to nine plications were still in place with reduced gastric volume in all 17 patients at the 12-month follow-up. Adverse events including gastric pain, sore throat, diarrhea, nausea, constipation, and vomiting were mild and resolved with conservative treatment. No serious adverse events occurred. Compared with TERIS, ACE has the advantage that no foreign body is implanted, so there is no need for a removal procedure. The study and related trials are limited, making evaluation of this procedure difficult. ACE is still in clinical trials and without FDA approval.[2]

Delaying gastric emptying

Gastric botulinum toxin A injection

Botulinum toxin A (BTA) is an acetylcholinesterase inhibitor that is a long-acting inhibitor of both voluntary and smooth muscle contraction, leading to a reversible paralytic effect. It can paralyze the stomach temporarily, delaying gastric emptying by moderating the propulsive contraction effect of the antral pump.[2]

Preclinical animal studies were initially conducted in rats. Significant weight loss as well as the feasibility and safety of the injections were demonstrated.[43,44] Due to the equivocal data of mucosal-based gastric BTA injection therapy, some investigators began to emphasize submucosal BTA injection into the muscularis propria. A study performed by Topazian *et al*.[45] in 2008 showed that, at a 16-week follow-up, the average weight loss was 4.9 ± 6.3 kg that was achieved without any permanent damage. Its effect, however, was lost gradually over the first 3–6 months. Furthermore, significantly delayed gastric emptying was found in a cohort receiving a 300-unit BTA injection in the randomized sham-controlled trial conducted in 2013.[46] More recently, however, a systematic review and meta-analysis of BTA injection concluded that treatment of obesity with BTA is not effective.[47]

Transpyloric shuttle

The transpyloric shuttle (TPS; BAROnova, Inc., Goleta, CA, USA) is a large, spherical silicone bulb tethered to a small, olive-sized cylindrical bulb. It is introduced into the stomach through a flexible, elongated sheath. Normal physiologic gastric peristalsis can push the distal cylindrical bulb into the proximal duodenum. The large bulb cannot get through the pylorus and remains in the stomach. The tether traverses the pylorus, keeping the bulbs connected. Due to gastric peristalsis and compliance of the large bulb, the bulb can obstruct the pylorus intermittently and then retreat into the stomach, allowing the gastric contents to get through the pylorus. Furthermore, the large bulb also acts as a space-occupying device, reducing the functional gastric volume, just like IGB. The TPS must also be removed after a period of time. Based on the results of the recent experiments, the best placement interval is 6–12 months.[2]

Marinos *et al*.[48] conducted a clinical trial in 2014 confirming the feasibility, safety, and efficacy of TPS. A total of twenty patients were enrolled. At 3- and 6-month follow-up, the %EWLs were 25.1% and 41.0%, respectively, and 90% of the patients had achieved maximum weight loss at the time of device removal, highlighting the long-term weight loss potential of TPS. Half the patients, however, were found to have antral ulcers. Eight of the patients received proton pump inhibitor treatment with ulcer resolution, but two patients were symptomatic and underwent early device removal. A randomized, double-blinded, sham-controlled clinical trial is ongoing with the goal of FDA approval.[48]

Altering gastric wall compliance

Endoscopic bariatric surgery can be used as a primary treatment for obese patients as a presurgical procedure and for the treatment for complications after bariatric surgery. It can also be used as a secondary treatment, as in weight gain, one of the common complications of RYGB. Furthermore, many acquired anatomical abnormalities can also lead to obesity such as gastric-gastric fistula and dilated GJ anastomosis. In view of these circumstances, anastomotic reduction can delay gastric emptying and curb weight regain.[49]

Endoscopic sclerotherapy

Endoscopic sclerotherapy affects the anastomotic compliance and thus delays gastric emptying in patients suffering from stoma dilation and post-RYGB weight gain. A sclerosant such as morrhuate sodium can be injected into the GJ aperture, inciting an inflammatory reaction with edema and subsequent fibrosis, thus reducing stoma diameter.

In a clinical trial conducted by Spaulding[50] in 2003, twenty patients with a dilated GJ stoma were enrolled and received endoscopic sclerotherapy. Reduction of the diameter of the gastrojejunostomy to 9–10 mm was achieved in all patients.

As many as 15 patients lost weight, with an average weight loss of 5.8 kg in 2 months. This test verified the feasibility and safety of endoscopic sclerotherapy. A retrospective study conducted by Abu Dayyeh *et al*.[51] in 2012 showed that, at 6 and 12 months from the last sclerotherapy procedure, weight regain stabilized in 92% and 78% of all 231 patients, respectively. Those who underwent two or three sclerotherapy sessions had significantly higher rates of weight-regain stabilization than those who underwent a single session. Another study of 34 patients showed that the %TBWL was 2.7 ± 5.5 and 6.1 ± 6.8 at 3 and 6 months, respectively.[52]

Endoscopic sclerotherapy has the benefit of being a minimally invasive, cost-effective, and technically facile procedure. It is one of the main therapeutic options in alleviating weight regain after RYGB. The common complications related to morrhuate sodium use, such as hypersensitivity reaction, ulcer formation, and bleeding, require vigilance, especially for patients with cardiovascular comorbidities or coagulopathy.[52] Long-term safety and weight-loss outcomes are being assessed.

Radiofrequency ablation

Radiofrequency ablation applies thermal energy directly to the gastrointestinal mucosa. A series of RFA treatments of the after-RYGB gastric stoma and GJ aperture may alter the compliance, reduce the stoma diameter, and promote weight loss.

In a clinical trial conducted by Abrams *et al*.[53] in 2017, 25 patients with weight regain after RYGB were registered. These patients received RFA every 4 months, up to three treatment sessions in total. At 12-month follow-up, the mean post-RFA %EWL was 30.4%, confirming the effect of RFA on after-RYGB weight loss. About 40% of patients, however, had complications such as abdominal pain and vomiting, similar to the complications of RFA of the esophagus. The sample size was too small to determine whether the adverse event rate is markedly different from that of esophageal RFA. Additional studies with larger sample sizes are needed to demonstrate the safety and long-term weight loss effect of RFA.

Altering food absorption

The endoscopic duodenal-jejunal bypass sleeve (EDJBS) was first reported by Rodriguez-Grunert *et al*.[54] in 2008. The EDJBS consists of an implant that is endoscopically delivered and anchored in the proximal duodenum and a sleeve that is extended into the jejunum. Chyme passes through the sleeve, making an intestinal bypass/biliopancreatic diversion without the need for stapling or anastomosis. A randomized controlled trial conducted by Koehestanie *et al*.[55] in 2014 showed that the %EWL of the test group and diet control group were 32.0% and 16.4%, respectively, after 6-month follow-up. The blood glucose was also found to be satisfactorily controlled.

The endoscopic gastroduodenojejunal bypass sleeve is also designed to achieve weight loss by virtue of sleeve placement in the digestive tract. The sleeve is about 120 cm long, and it can be placed at the junction of the gastroesophageal extension to the proximal jejunum. Clinical trials conducted by Sandler *et al*.[56] in 2011 showed that, in the 22 patients, five had the sleeves within 3 weeks because of pharyngeal discomfort. The remaining patients completed the 12-week follow-up. The average weight loss was 16.8 kg, and the %EWL was 39.7%. In addition, diabetes, hypertension, hyperlipidemia, and other complications were satisfactorily controlled. In another trial with 12 patients over a 12-month period, ten patients completed the trial with a %EWL of 35.9% at the end of the year. Two patients were unable to tolerate the device and required early removal. Of note, however, four patients had partial cuff detachment at the time of removal and experienced less weight loss.[57] Although the weight loss was significant, complications such as shifting of the sleeve, abdominal pain, sore throat, and the instability of the device may be the biggest obstacles that need to be overcome.[58]

Summary and Expectations

The technology of bariatric and metabolic endoscopy has developed rapidly in recent years, and many new endoscopic devices have been introduced. The IGB, with its comparatively long period of development, is the most mature and widely used device. With an increasing number of novel innovations applied in the real, clinical world, we are optimistic about a brighter future for minimally invasive techniques to combat obesity. Due to the lack of clinical data and shortage of clinical experience and instruction in the use of this new equipment, additional dedicated research is required for advancement in this field. Endoscopic bariatric surgery is thriving, endowing both physician practitioners, and their patients with more alternatives for customized therapy with optimal results achieved and fewer complications.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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