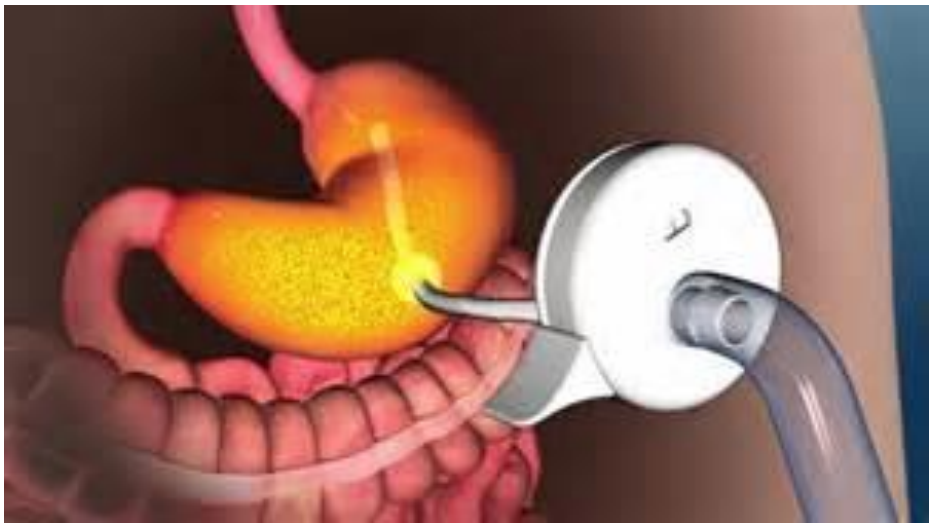
UT SOUTHWESTERN INTERNAL MEDICINE GRAND ROUNDS

Advances in the Endoscopic Management of Obesity



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This is to acknowledge that Byron Cryer M.D. has disclosed that he does have financial interests or other relationships with commercial concerns relating indirectly to this program. Dr. Cryer will be discussing off-label uses in his presentation.

Name of Presenter: **Byron Cryer, M.D.**

Academic Rank: **Professor, Department of Medicine, Division of Digestive Diseases**

Administrative Title: **Associate Dean, Faculty Diversity and Development**

Interests:

Dr. Cryer's clinical interests are in general gastroenterology. His specific areas of interest are acid-peptic diseases of the upper gastrointestinal tract. His primary research interest has been in the pathogenesis of peptic ulcer disease. Dr. Cryer's research focus has been clinically oriented in that he has exclusively studied the pathophysiology of these processes in humans. His recent investigations have explored the mechanism of gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) within the stomach and duodenum. The most recent aspect of NSAID investigation has been an evaluation of the cyclooxygenase (COX)-2 specific NSAIDs.

Purpose and Overview:

Obesity has become a worldwide epidemic with significant impact on quality of life, morbidity, and mortality rates. Over the past two decades, bariatric surgery has established itself as the most effective and durable treatment for patients with obesity and its associated comorbidities. However, despite the use of minimally invasive techniques, bariatric surgery is associated with complications, has a substantial cost and is used by only 1% of patients who are eligible. Therefore, there is a need for effective minimally invasive therapies, which will be utilized by the large proportion of obese patients who are in desperate need of treatment but are not receiving any. Endoscopic approaches to the management of obesity have been developed, with the aim of delivering more effective, durable, and safer methods of weight reduction.

The purpose of this Internal Medicine Grand Rounds is to provide an overview of currently available and future endoscopic therapies likely to be used in the management of obesity.

Learning Objectives

Upon completion of this session, the participant should be able to:

1) Discuss the variety of Endoscopic Bariatric Therapies (EBT's) that are being developed as alternatives to Bariatric Surgery.
2) Identify the risks and benefits of EBT's and weigh them against surgery.
3) Explain the efficacy of these EBT's in treating obesity and its co-morbidities, like type 2 diabetes.

Introduction

Obesity is a complex chronic disease which results in increased morbidity and mortality. Its growing prevalence and associated comorbidities, particularly the development of type 2 diabetes mellitus, have had a significant impact on quality of life and impose a large economic burden on healthcare systems. The treatment of obesity remains a difficult clinical problem and, despite initial weight loss, maintaining a healthy weight is not possible in the majority of patients. Currently, accepted therapies for the management of obesity include dietary modification, physical exercise, pharmacological treatment, surgical therapy, and, more recently, endoscopic treatment.

Dietary and lifestyle modification often fail to achieve the desired weight loss outcomes. Pharmacological therapies are often associated with contraindications and low rates of compliance. In the United States, the National Institute of Health recommends weight loss surgery as an option for carefully selected individuals with a body mass index (BMI) of ≥40 kg/m^2 or those with a BMI of ≥35 kg/m^2 with significant comorbidities, who have failed diet, exercise, and drug therapy.

Bariatric Surgery – the best way to lower rates of obesity?

Several surgical approaches, collectively referred to as “bariatric surgery”, have been successfully used to treat obesity. In a systematic review and meta-analysis of randomized controlled trials, there were greater weight loss and higher remission rates for type 2 diabetes mellitus in the bariatric surgery group compared to lifestyle modification alone. Newer laparoscopic bariatric surgical techniques provide multiple advantages over older, open surgical methods. These include lower postoperative adverse events, earlier ambulation after surgery, and reduced length of hospital stay . Notably, bariatric surgery is associated with a significant improvement in comorbidities and has been proven to reduce mortality.

Despite the clear benefits of bariatric surgery, there are some pitfalls. Importantly, bariatric surgery is associated with significant morbidity and substantial costs. In addition, bariatric surgery is not available to patients with a BMI <35 kg/m^2 even if clinically significant comorbidities (metabolic, psychological, etc.) exist. Additionally, only a minute proportion of patients who qualify and would conceivably benefit from bariatric surgery ever undertake it. Finally, the durability of bariatric surgery has recently been questioned with weight regain being not uncommon.

Current research is focused on the development of alternative methods of obesity treatment that are less invasive, more cost-effective, and associated with a lower operative risk. Such methods should also be efficacious, durable, repeatable, reversible, and safe. Endoluminal interventions or Endoscopic Bariatric Therapies (EBTs) performed entirely through the gastrointestinal (GI) tract, using flexible endoscopy, offer the potential for ambulatory weight loss procedures that may be safer and more cost-effective than current laparoscopic approaches.

Endoscopy has a well-established role in the preoperative evaluation of patients undergoing bariatric surgery and in the assessment and management of surgical complications. In addition, endoscopic procedures have been used as a “bridge to

surgery" in order to reduce obesity related operative risks. However, endoscopic therapies as a primary treatment modality for obesity have only more recently been explored. Endoscopic modalities in the treatment of obesity can be categorized into the following: space-occupying devices, gastric restrictive methods, malabsorptive endoscopic procedures, regulating gastric emptying, and other therapies. Of these methods, the most commonly employed are space-occupying devices.

While gastric surgery, like laparoscopic and open Roux-en-Y gastric bypass (RYGB), adjustable gastric band, gastric sleeve, vertical banded gastroplasty, duodenal switch, and biliopancreatic diversion, all tend be to the most effective and durable way of treating obesity (and opening the way for improvement of obesity's co-morbidities), not even 1% of qualifying potential bariatric surgery patients actually undergo these procedures. There are now a wide variety of such treatments already under testing and development.

Endoscopic Bariatric Therapies (EBT's):

There are many EBTs under development. EBTs are low-risk, fast, and easily accessible.

Two main branches of EBT's have been developed: Gastric Endoscopic Interventions and Small Bowel Endoscopic Interventions ***(*Figure 1*)***.

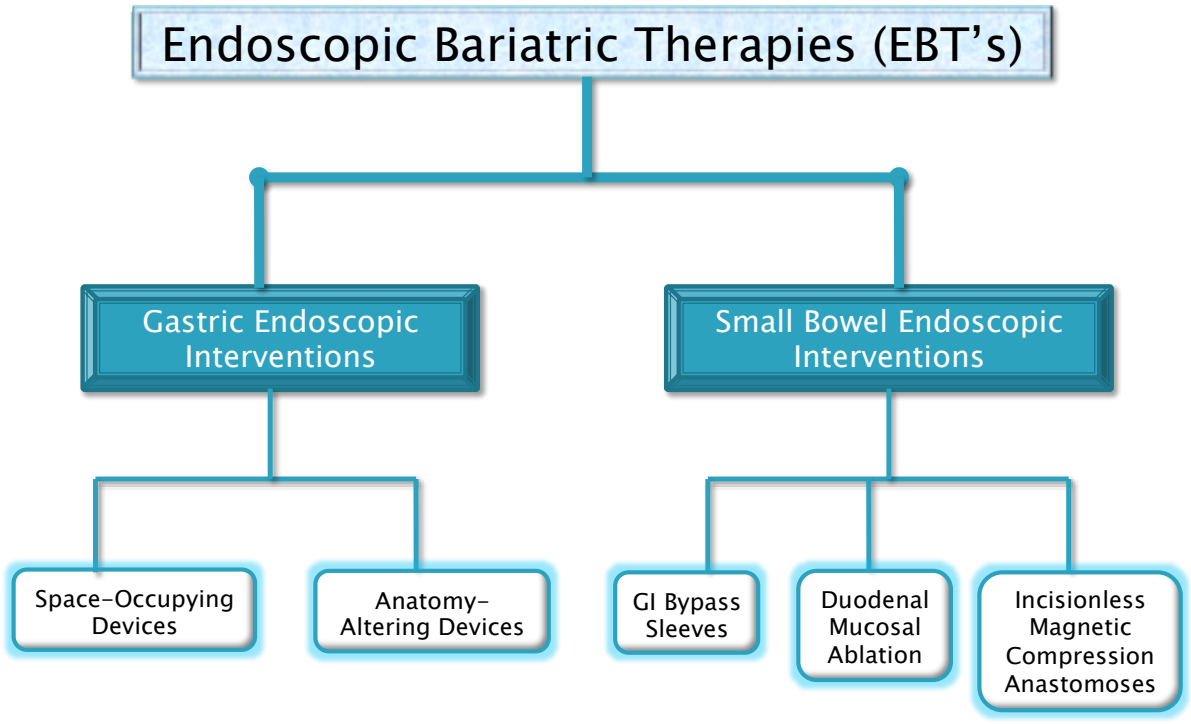


Figure 1: Endoscopic Bariatric Therapeutic devices under development.

Gastric Endoscopic Interventions

- Space-Occupying Devices: These devices typically take the form of one or more intragastric balloons, endoscopically placed in the stomach. They are filled after gastric positioning. The filling differs between devices, but can include saline, dyed-solution, or even gas. Other space-occupying devices include gastroesophageal stents and funnel-like devices that block the pylorus and delay gastric emptying.

- Anatomy-Altering Devices: This category can include Aspiration Therapy. During Aspiration Therapy an "Aspire Assist Device" is used to "aspirate" the stomach, flushing out about 30% of an ingested meal through a percutaneous gastrostomy "A-tube." Gastroplasty techniques are also included. Another examples example is the endoscopic suturing of the stomach, along its greater curvature, to create a sleeve.

Space-Occupying Devices:

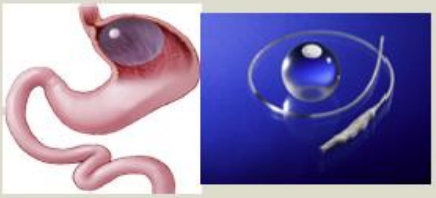
Intragastric Balloons

Intragastric balloons (IGB) have been used in the treatment of obesity for the last 20 years with a large body of evidence supporting its short-term efficacy and safety.

Initial balloons constructed from gum and latex were not resistant to gastric acid and deflated quickly. The Garren-Edwards gastric bubble (American-Edwards Laboratories, USA) was an air-filled polyurethane balloon that was approved by the US Food and Drug Administration in 1985. The balloon was widely used for several years but was later withdrawn from use when several studies demonstrated its lack of superiority to diet and behavioral therapy. These balloons were also associated with a large number of serious complications including mucosal erosion (26%), gastric ulcer (14%), and small bowel obstruction (2%).

Intragastric balloons became commercially available in 1991 and is the most commonly used balloon for weight loss. It is constructed from a silicone elastomer. The balloon is inserted under endoscopic control into the gastric fundus under light sedation (**Figure 2**). The balloon is filled with between 400 and 700 mL of normal saline/methylene blue solution via a catheter.

Intragastric Balloons (**Figure 2**)

Intragastric Balloons (IGB)		
Orbera Apollo Endosurgery		Elastic spherical balloon made from silicone and filled with about 500-700 ml of saline. It is inserted and retrieved endoscopically.
ReShape Duo ReShape Medical		Saline solution-filled, dual intragastric balloon system with 2 balloons attached to each other by a flexible tube. Each balloon has independent channels so that unintentional leaks or deflation in 1 balloon do not to impact the other balloon.
Spatz Adjustable Balloon System Spatz Medical		Saline filled intragastric balloon with an extractable inflation tube for volume adjustment, while the IGB remains in the stomach.
Obalon Gastric Balloon Obalon Therapeutics		Gas-filled balloon with a maximal volume of 250ml. It is compressed, folded, and fitted in a large gelatin capsule. Once the capsule is ingested, the catheter extends from the stomach to outside the body through the esophagus and the mouth. After balloon inflation, the catheter is detached and removed. One or more balloon can be swallowed during the same session.

The balloon has been used in those with a body mass index of 40 kg/m^2 or greater, serving as a pretreatment to bariatric surgery with the aim of reducing anesthetic risk and surgical complications. Other indications include those with lower BMIs with significant comorbidities or in those patients that have contraindications to bariatric surgery.

The balloon should be removed after a maximum of six months, beyond this period; the risk of spontaneous balloon deflation significantly increases. The procedure for balloon removal is also performed under sedation. The balloon is punctured with a needle, and the saline is emptied via a catheter. The balloon is removed using grasping forceps or a polypectomy snare.

Several investigators have evaluated the efficacy of the gastric balloon in the management of obesity. In the largest series of gastric balloon patients so far, Genco et al. in a study of 2,515 patients had reported a percentage excess weight loss (%EWL) of 33.8% ± 18.7% at 6 months of follow-up. In this period, there was improvement or resolution of diabetes and hypertension in 86.9 and 93.7% of patients, respectively. The complication rate was acceptable at 2.8%.

A recent systematic review of the literature reported on the efficacy of the gastric balloon (now marketed as Orbera (Apollo Endosurgery, Austin, TX) in obese patients. The review identified 7 studies (409 patients) which reported weight loss at 6 months with a mean EWL of 16 kg. Interestingly, 80% of weight loss was found to occur in the first 3 months of therapy. The durability of this technique is questionable, as demonstrated by Dastis et al. who demonstrated that only a quarter of individuals maintained weight loss up to 30 months after procedure.

Two other balloons are now commercially available and these have been specifically designed with antimigration properties. The ReShape Duo (ReShape Medical, San Clemente, CA) consists of two closely attached, independently fluid filled balloons approved for 6-month implantation. The Spatz Adjustable Balloon (Spatz Medical, Great Neck, NY) has an attached catheter to prevent migration and an extractable injection tube for volume adjustment. The adjustable nature theoretically enables the balloon volume to be titrated to tolerability and efficacy. The limited data available on these two balloons show similar efficacy and safety to the Orbera.

The most common complications include nausea and vomiting which can persist for up to a week in two-thirds of patients. This can be often effectively managed pharmacologically. Other adverse events include gastric erosion and ulceration. In case of spontaneous balloon deflation, the methylene blue is absorbed and excreted by the kidneys causing green coloration of urine. The location of the balloon must then be verified radiologically and removed endoscopically in order to prevent subsequent small bowel obstruction.

Anatomy-Altering Devices

Transoral gastroplasty is an example of a gastric restrictive procedure, in which suturing or stapling results in gastric partition. Several endoscopic suturing and stapling devices have been developed.

The Endocinch (C.R. Bard, Inc., Murray Hill, NJ) device has been used for endoluminal vertical gastroplasty (**Figure 3**). This technique involves the use of a suturing device contained within a capsule that is attached to the end of a diagnostic gastroscope. After suctioning tissue into the capsule, a preloaded suture is advanced through the captured tissue. Sutures are deployed in a continuous and cross-linked fashion from the proximal fundus to the distal body of the stomach to create a narrow tube-like passage. Fogel et al. first described the use of this device in 64 obese patients. In that study, 97% of patients achieved >30 %EWL at 12 months of follow-up and the mean %EWL overall was 58% ± 20%. At 12 months, upon repeat endoscopy, only 2 required additional intervention, demonstrating the durability of this technique. There were minimal complications, and patients were discharged on the day of the procedure.

Figure 3

An updated version of the device, the RESTORe Suturing System (Bard/Davol, Warwick, RI), has been evaluated in the TRIM trial. This trial was designed in an attempt to validate previously demonstrated degrees of weight loss, with the addition of close clinical and endoscopic follow-up. But, unlike the Endocinch, this device was unable to create a continuous suture pattern owing to suture tension. As a result, this device produced only modest decreases in weight with a mean %EWL of 27.7% ± 21.9% at 12 months of follow-up. Durability was poor with endoscopy at 12 months of follow-up demonstrating partial or complete release of plications in 13 of 14 patients. Modification in suturing techniques or early endoscopic follow-up with repeated interventions may potentially provide a more long-lasting weight loss effect. The procedure was well tolerated without serious adverse events. Of note, neither of the two aforementioned studies included a control group and likely a significant placebo effect related to the procedure and the close monitoring that occurs during a clinical trial influences outcomes.

The TOGA system (Satiety Inc., USA) is a specifically designed device that enables the creation of a stapled, restrictive pouch along the lesser curvature of the stomach under direct endoscopic visualization. The procedure is performed under general anesthesia with an average procedure time of 2 hours. The TOGA sleeve stapler is introduced over a guide wire into the proximal stomach. A endoscope is advanced through the device and retroflexed to directly visualize the stapler. Tissue is gathered into the stapler using suction and staples are delivered. This process can be repeated in order to further narrow the lumen of the sleeve. By slowing the

movement of food through the stomach and limiting the ability of the stomach to expand, early satiety is achieved.

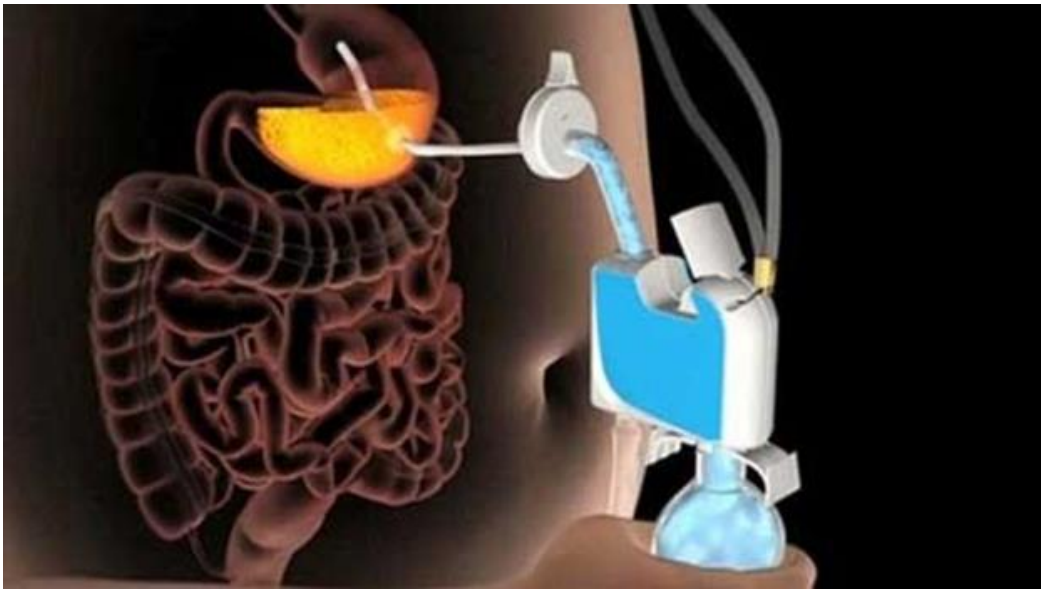
Since initial studies conducted by Deviere et al., refinement of technique has resulted in improved outcomes with fewer complications. A prospective, multicenter trial of 67 patients demonstrated 38.1 ± 17.1 % EWL at 12 months with 79% of the study population completing 1-year follow-up. Additionally, improvements in such indices including HbA1c% and triglyceride levels were observed. Most common adverse effects included transient epigastric pain, nausea, and vomiting. More serious complications included one case of respiratory insufficiency and another of pneumoperitoneum, which resolved with conservative management. In 79% of patients who completed one-year follow-up, staple line dehiscence remained a problem, occurring in 50% of patients. Unfortunately, Satiety Inc., the manufacturer of this device, recently declared insolvency and the future of this promising technique is uncertain at this point of time.

In 2013, a study by Abu Dayyeh et al. reported a newer endoscopic suturing device (Overstitch; Apollo Endosurgery, Austin, TX) to perform free hand, full thickness, transoral endoscopic gastric volume reduction in 4 obese patients. In this uncontrolled trial, technical feasibility was demonstrated. The procedure time was over three hours but no intraoperative adverse events were observed. Postprocedural abdominal pain and nausea developed in three patients. Using the same device, a more efficient variation of the suture technique using 8 to 10 sutures has been reported by two groups. A study by Sharaiha et al. performed the same procedure on 10 patients and observed an EWL of 18%, 26%, and 30% after 1, 3, and 6 months, respectively. Another study by Lopez-Nava et al. reported a study in 20 patients and observed an EWL of 29%, 39%, and 54% at 1, 3, and 6 months, respectively. They both concluded that this approach might provide a cost-effective outpatient procedure to add to the steadily growing armamentarium available for treatment of obesity.

Aspiration Therapy

Aspiration therapy is a relatively new technique that involves endoscopic placement of a gastrostomy tube (A-tube) and the Aspire Assist siphon assembly (Aspire Bariatrics, King of Prussia, PA) to aspirate gastric contents 20 minutes after meal consumption (**Figure 4).** A pilot study by Sullivan et al. of 18 obese subjects demonstrated the effectiveness of this technique. After 12 months, subjects in the aspiration therapy group had a %EWL of 49.9% ± 7.7% compared to those with lifestyle therapy alone who achieved a %EWL of 14.9% ± 12.2%. This weight loss was maintained for a further year in 7 of 10 patients who continued with the therapy. The study reported no adverse effects of aspiration therapy on eating behavior and no evidence of compensation for aspirated calories with increased food intake.

Figure 4. Aspire Assist Device



A more recent study by Forssell et al. demonstrated the effectiveness of this device in 25 obese men and women who had the AspireAssist™ gastrostomy tube placed after 4 weeks of taking a very-low-calorie diet. At 6 months, mean weight loss was 16.5 ± 7.8 kg in the 22 subjects who completed 26 weeks of therapy. The mean %EWL was 40.8 ± 19.8%. No serious complications occurred.

Small Bowel Endoscopic Interventions:

- GI Bypass Sleeves: These sleeves can prevent food from being digested by bypassing the duodenum or even the stomach and duodenum, typically emptying into the jejunum.

- Duodenal Mucosal Ablation: The mucosa of the duodenum is ablated with specialized radiofrequency ablation technology. Once ablated, the duodenum can be repopulated with mucosa from the jejunum.

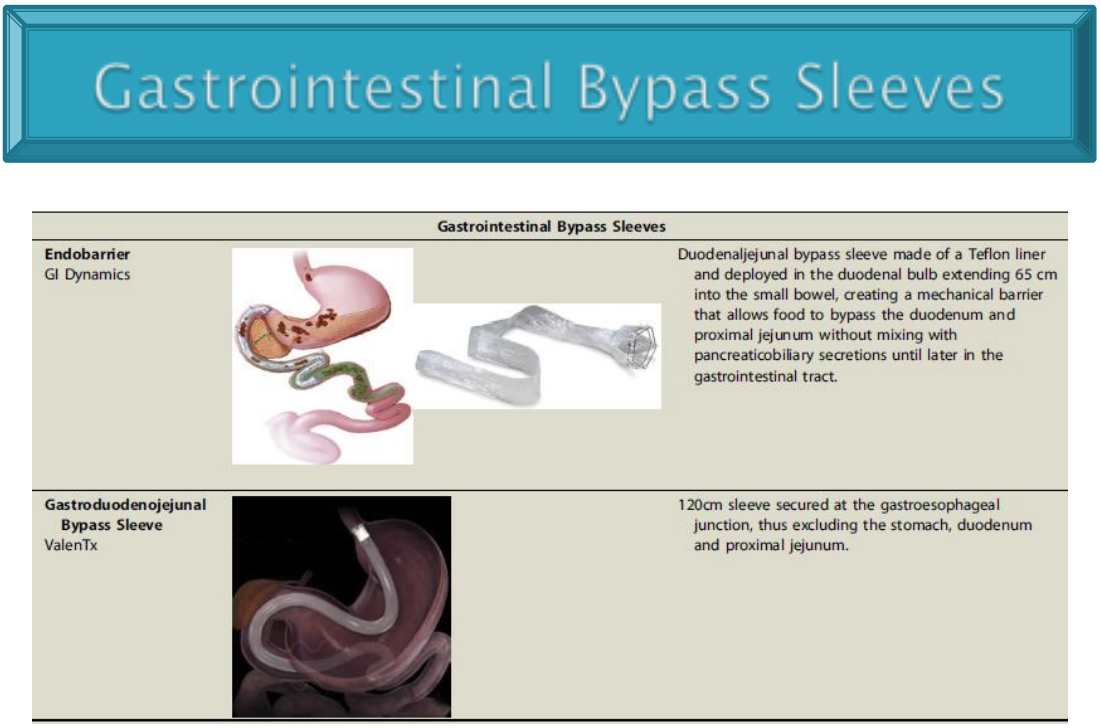
- Incisionless Magnetic Compression Anastomeses: Here, self-assembling magnets are used to connect various possible small bowel locations. Once the magnets are placed, and attach one area to the corresponding other area of the small bowel, the tissue surrounded by the magnets undergoes necrosis, while the tissue outside the magnets is remodeled. This creates an anastomosis for the for food to bypass the specified area of the small bowel during digestion.

Duodenal-jejunal bypass liner

Duodenal-jejunal bypass liner (DJBL) was designed as a nonsurgical approach that enabled components of the Roux-en-Y procedure, namely, exclusion of the duodenum and proximal jejunum and exposure of the distal jejunum to undigested nutrients, reducing absorption and preventing the action of biliary and pancreatic secretions (**Figure 5**). This action intervenes with the body's metabolic functions, including alteration of incretin pathways resulting in weight loss and improved insulin sensitivity.

The EndoBarrier gastrointestinal liner (GI Dynamics Inc., Lexington, MA, USA) is a flexible, nutrient-impermeable 60 cm sleeve that is anchored in the duodenal bulb and extended into the proximal jejunum deployed using dynamic fluoroscopy. The anchor is a self-expanding stent that enables fixation within the duodenal bulb. The sleeve is maintained from 3 months to 12 months after fixation.

Figure 5



Abu, B. K., Edmundowicz, S. A., Jonnalagadda, S., Kumar, N., Larsen, M., Sullivan, S., ... & Banerjee, S. (2015). Endoscopic bariatric therapies. *Gastrointestinal Endoscopy*, *81*(5), 1073-1086

The first reported human case series was by Rodriguez-Grunert et al. in 2008, which reported a 12-week %EWL of 23.6%. Three other studies have completed trials in a randomised fashion against either sham endoscopic procedures or low energy diets. They reported 12-week %EWLs, ranging from 11.9% to 22% with statistically significant weight loss compared with controls.

Two reports describe longer-term use of the DJBL in obese and diabetic patients. Escalona et al. in a single-arm prospective open-label study reported a mean %EWL of 47% in 24 patients that completed the 52-week program. de Moura et al., in a similarly designed study, used a 52-week HbA1c% as their primary endpoint. This study demonstrated a decrease in HbA1c% of 2.1% ± 0.3%, suggesting a significant effect on diabetes.

These promising results confirmed a recently conducted randomized control trial by Koehestanie et al. in which 70 patients with obesity and type 2 diabetes mellitus were included. Thirty-eight patients were randomized to the DJBL treatment in combination with dietary intervention and 39 controls received dietary intervention alone. At 26 weeks, the DJBL group has a %EWL of 32% (22.0%–46.7%) compared to 16.4% (4.1%–34.6%) in controls. The device was removed at 6 months, and follow-up continued to 52 weeks. At this time, the DJBL group has a %EWL of 19.8% (10.6%–45.0%) compared to 11.7% (1.4%–25.4%) in controls. In addition, the HbA1c% improved to 7.0% (6.4%–7.5%) in the DLBL group compared to 7.9% (6.6%–8.3%) in controls at 6 months.

Importantly, recent systematic reviews have identified a lack of data regarding the durability of the DJBL. There are no studies that examine the effects of the device beyond 52 weeks. The effects of the DJBL on weight loss and diabetes control beyond 52 weeks will need to be investigated further .

The device is complicated by a high implantation failure rate of approximately 20% due to anatomical reasons, namely, a short duodenal bulb, and rarely due to investigator inexperience. Complications associated with the procedure most commonly include nausea and upper abdominal pain, which resolved with pharmacological management. More serious complications including device migration and gastrointestinal bleeding require early device extraction. Further studies are needed to analyze the incidence of such complications.

Efficacy for the treatment of obesity:

- Over the wide array of devices in development, most perform very well when it comes to immediate, short-term weight loss (especially when combined with good diet and exercise).

- **Figure 6** depicts the success of the Duodenal-Jejunal Barrier Sleeve in particular, over the, relatively stable, sham group throughout the 12 weeks of this study's treatment.

Figure 6

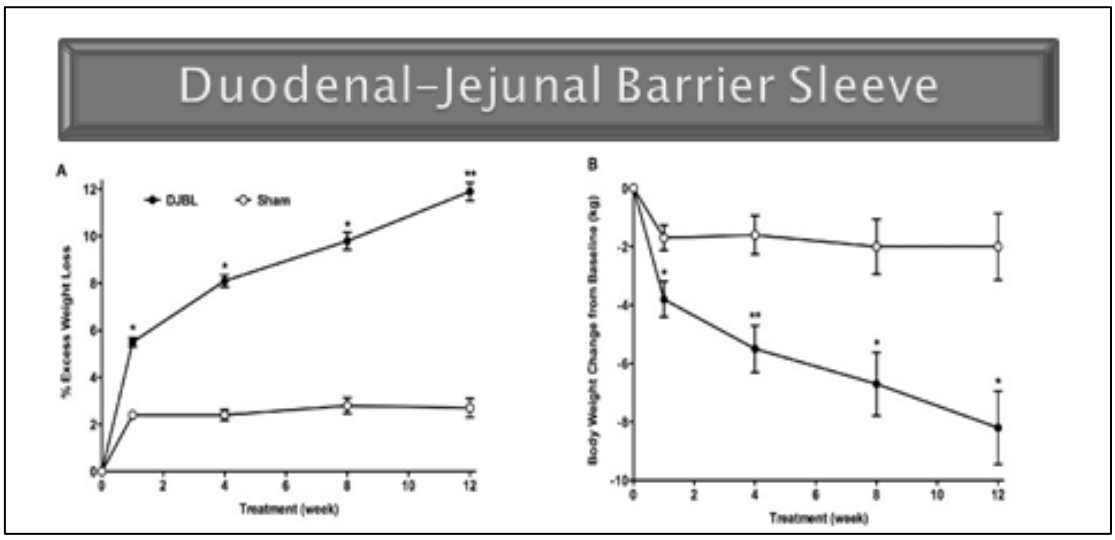


Figure 6: Data depicting the % excess weight loss (A) and body weight change from baseline (kg) over the course of the treatment in a sham group versus a Duodenal-Jejunal Barrier Sleeve group.

Efficacy for the treatment of obesity's co-morbidities:

- Obesity can cause multiple co-morbidities. These can include diabetes, dyslipidemia, hypertension, coronary heart disease, stroke, sleep apnea, osteoarthritis, gallbladder disease, nonalcoholic fatty liver disease (NAFLD), and cancer.

- Eighteen people participated in a randomized, blinded pilot study for the Duodenal sleeve. Twelve of them received the Duodenal Sleeve, while 6 of them were put into the sham group. They were all followed-up with for a 24 week period.
    - The results indicated diabetic patients showed improvement after Duodenal-Jejunal Bypass Liner implantation. **(Figure 7)**

Figure 7

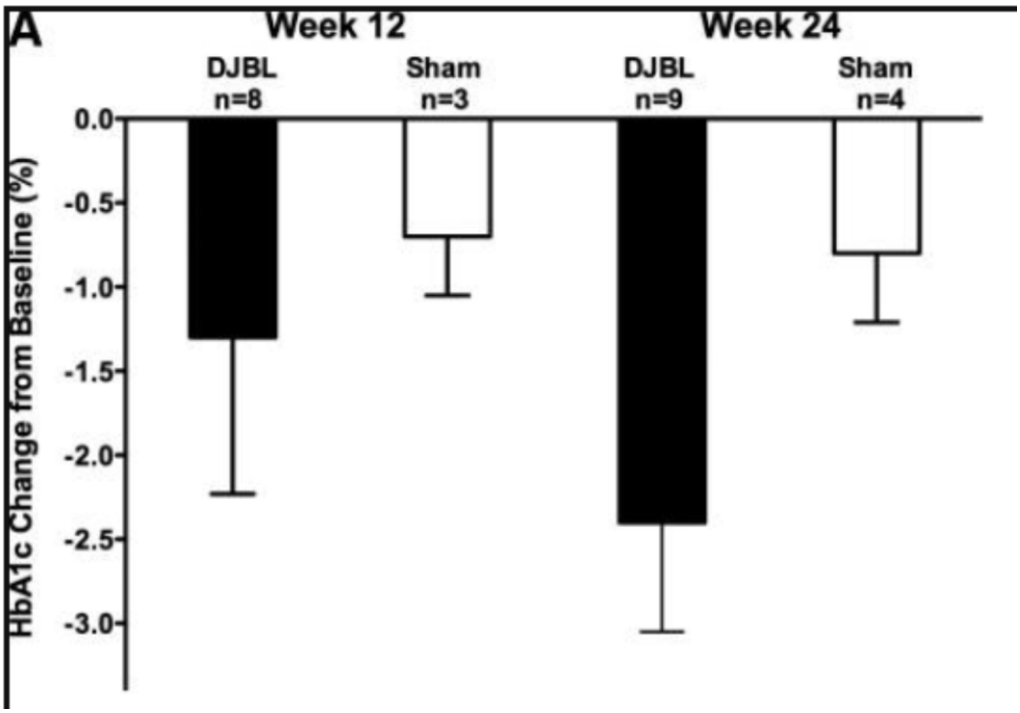


Figure 7: Change in HbA_{1c} from Baseline. There was a 9.3% ± 0.6% change in HBA_{1c} from baseline in the "Duodenal-Jejunal Bypass Liner" arm, while the "Sham" arm only had an 8.8% ± 1.2% change in HBA_{1c}.

- While diabetic conditions improved, it should be noted that there was a very small number of subjects.

- Three of the 12 devices also had to be removed because of both abdominal pain and migration of the DJBL's liner from its initial anchor site.

- The DJBL still holds great promise as a temporary and repeatable treatment method for obesity and Type 2 DM.

Conclusions

Obesity and its associated comorbidities are on the rise worldwide, reaching epidemic proportions. To meet this challenge, the field of bariatrics has been growing with the development of minimally invasive surgical procedures. These, however, are subject to considerable cost, limited patient applicability, and substantial risks. Newer bariatric endoluminal interventions have broadened the range of treatment and allow gastroenterologists to play a greater and perhaps central role in the management of obese patients. Preliminary results of these interventions are promising, yet many questions remain regarding the safety and efficacy of such therapies. Additionally, with ongoing innovation, paralleled with clinical research, new treatment options for the endoscopist are on the horizon.

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