



# Innovations in gastroesophageal reflux disease interventions – fundoplication, magnets, and endoscopic therapy

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**Abstract:** Gastroesophageal reflux disease (GERD) is a commonly encountered condition that is characterized by reflux of gastric contents into the esophagus. The condition has been increasing in prevalence, especially in the Western hemisphere, affecting millions of people worldwide. While lifestyle modifications and proton pump inhibitors (PPIs) have been the mainstay treatment, long-term PPI use may cause significant and unwanted side effects in susceptible populations and can include bone loss, *Clostridium difficile* infection, diarrhea, gastric polyps, and hypergastrinemia among other ailments. Laparoscopic anti-reflux surgery (LARS) is a safe alternative to PPIs for patients with poorly controlled symptoms, structural abnormalities such as paraesophageal hernias, or those who simply do not wish to take life-long medication. Though LARS are low risk procedures and equivalent, if not superior to PPIs in multiple trials, there are many unwanted side effects including dysphagia, gas-bloat syndrome, slippage, migration, and recurrence. Therefore, alternative, less-invasive treatment methods have been gaining interest and popularity in the recent years. The most common procedures are magnetic device to augment the lower esophageal sphincter (LES), delivery of radiofrequency energy to the LES, transoral incisionless fundoplication (TIF), as well as anti-reflux mucosectomy (ARMS). This article will review alternative and innovative GERD therapies while comparing their effectiveness to standard treatments.

**Keywords:** Endoscopy; fundoplication; gastroesophageal reflux disease (GERD); obesity

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## Introduction

Gastroesophageal reflux disease (GERD) is a multifactorial, chronic relapsing condition defined as reflux of gastric contents into the esophagus and is the most common gastrointestinal disorder in the West (1,2). It affects up to 20% of population with peak prevalence between 30 to 60 years old, usually presenting with intermittent heartburn or regurgitation (1,3). However, it can also present with atypical symptoms such as chest pain or chronic cough. Complications from GERD are more commonly seen in men and the elderly and include esophagitis, Barrett's

esophagus, as well as stricture formation (1).

In order to alleviate symptoms and prevent complications, proton pump inhibitors (PPIs) have been the main treatment for GERD; however, many experience incomplete symptom relief or significant side effects and thus require alternative therapies. Additionally, direct annual cost to treat GERD is estimated to be \$10 billion and thus represents an important topic to address (4). Laparoscopic anti-reflux surgery (LARS) is the primary treatment option for refractory GERD and has been proven as effective as PPIs in multiple trials (5). LARS does carry some potential unwanted risks and thus

**Table 1** Original DeMeester composite score components (12)

	Optimal Threshold (mean $\pm$ SD)
Total time pH <4	<4.2% (1.478% $\pm$ 1.381%)
Upright time pH <4	<6.3% (2.33% $\pm$ 1.975%)
Supine time pH <4	<1.2% (0.286% $\pm$ 0.547%)
# Total episodes	<50 (20.6 $\pm$ 14.773)
# Episodes >5 minutes	3 or fewer (0.6 $\pm$ 1.241)
Longest episode	<9.2 min (3.866 $\pm$ 2.689) min

additional, less-invasive therapies have been coming to the forefront, which include the magnetic device for lower esophageal sphincter (LES) augmentation as well as a number of endoscopic therapies, including radiofrequency therapy delivery to LES, transoral incisionless fundoplication (TIF), and anti-reflux mucosectomy (ARMS) (6). The aim of this review was to look at the evolution of GERD treatment in order to highlight the new advances and review their safety.

### Pathophysiology

While some degree of brief reflux of gastric contents may be normal, it is generally prevented by an anti-reflux barrier, which is composed of LES and crural fibers of the diaphragm forming a high-pressure zone (7). This in turn acts as a flap-valve, which is created by intraluminal extension of the angle of His and is maintained in its anatomic position in order to allow overlap of the 2 structures via phrenoesophageal ligament and gastric cardia fibers (7,8). GERD becomes pathologic once the esophageal mucosal barrier exceeds its capacity to clear noxious stimuli following increased exposure (7). While mucosal changes may not necessarily be seen, the anti-reflux barrier is compromised (1,7). The etiology of GERD is multifactorial and can generally be categorized as influenced by structural or anatomical components, diet and lifestyle, or functional. Obesity, pregnancy, prolonged supine position, and certain diets that include alcohol and spicy foods all increase the likelihood of development of GERD. Functional problems that can lead to GERD include conditions that impair esophageal clearance through insufficient peristalsis, hypotensive resting tone, and transient LES relaxation following gastric distention (5). Structural problems on the other hand include those that create a defective anti-reflux barrier mainly due to the loss of the angle of His leading

to alteration of the LES pressure zone and are generally associated with hiatal hernia (HH) (1,9).

### Clinical presentation and diagnosis

The majority of patients with GERD present with typical symptoms including heartburn, regurgitation, chest pain, and dysphagia and are appropriately treated with diet and lifestyle intervention along with PPIs (10). It is important to recognize that GERD can also present with atypical symptoms such as chest pain along with occasional pulmonary manifestations of asthma, aspiration pneumonia, and lung damage (10,11). Occasionally, long-standing GERD is associated with alarming symptoms of weight loss and dysphagia (1).

While good history taking is crucial for GERD diagnosis, physical examination is often unremarkable and the symptoms are often non-specific (12). Thus, a variety of adjunct tests are often required for additional understanding of function and structure. Based on Jobe *et al.* consensus, such tests are crucial in order to objective the symptoms and tailor the appropriate management (12). One of the most common diagnostic tools, which remains the gold standard, is a 24-hour pH probe monitoring device that records acid exposure in the distal esophagus and correlates it with the patient's symptoms (13). The DeMeester Composite score is then calculated which characterizes the severity of GERD and a score >14.72 is diagnostic of prolonged acid exposure in the distal esophagus. The original components of the DeMeester Score are listed in *Table 1* (14). While the optimal values for each of the components are also listed in the table as this was a landmark article, it is important to keep in mind that some of the values have changed recently given larger studies that have been done. Additionally, the optimal value for the original Demeester Score that was used was 2 standard deviations (SD) higher than the mean value for control subjects (14).

Upper endoscopy is another useful adjunct that provides visual evaluation of the mucosal lining of the esophagus and is often the initial test performed to confirm GERD, though up to 50% of patients with GERD confirmed on pH probe will not have mucosal changes (11). Contrast esophagram may allow for identification of structural abnormalities, including presence of HH, stricture, or esophageal shortening, though upper endoscopy is often preferred (10). Lastly, high resolution esophageal manometry helps in identifying esophageal dysmotility that contributes to chronic GERD (10).

## Treatment modalities

Initial treatment of GERD includes lifestyle modifications (diet and exercise) and acid suppressive medications, including PPIs, histamine 2 (H2) receptor antagonists, and antacids (1). Many patients (up to 40%) are not able to achieve full remission despite medical management, and thus require an alternative for symptom resolution or remission (15). Intervention is also indicated for patients who experience significant side effects from PPIs, and those who do not wish to be on life-long medications (1). Regardless of treatment modality used, the goals remain the same and include symptom relief, mucosal healing, maintenance of remission as well as prevention of complications.

## Medical management

GERD therapy initially starts with lifestyle modification and often includes elimination of certain foods (acidic foods, carbonated drinks), avoiding meals right before bed, elevation of the head of bed, smoking and alcohol cessation and weight loss (16). However, if GERD symptoms still persist despite these changes, medical therapy is often initiated and generally consists of two categories: acid neutralizing (antacids) and antisecretory (PPIs and H2 blockers) (17). While antacids can be helpful with minor symptom relief, PPIs have remained the mainstay treatment in patients with typical GERD symptoms in the United States (US) since 1989 (1). PPIs are more effective than H2 blockers at symptom control and resolution of esophagitis since the PPIs block the final common pathway for acid production (17). It is important to note that if there is no symptom resolution despite increasing doses, an upper endoscopy should be performed 6 months after treatment in order to evaluate the anatomy (12). While effective, PPIs do have limitations as they do not address the dysfunctional anti-reflux barrier and many patients require escalating doses for long-term treatment; thus it is important to recognize the risks associated with long-term use. A variety of side effects have been attributed to PPIs and include rebound acid hypersecretion after discontinuation, bone fractures, hypomagnesemia, nutrient malabsorption, susceptibility to certain infections as well as chronic hypergastrinemia. In turn, conditions associated with chronic hypergastrinemia may increase the risk of developing gastric cancer and lead to vitamin B12 deficiency (18). Interestingly, the incidence of esophageal carcinoma has also increased since the introduction of PPI

and one study reported an association (19). Further research is warranted to describe a mechanism however, prolonged use of PPI is often a concern for patients. Thus, patients have sought surgical options for long-term management of GERD.

## Anti-reflux surgery

In 1955, Dr. Rudolf Nissen performed the first fundoplication for a patient with reflux esophagitis which was then published in 1956 (20,21). The procedure involved ligation of the short gastric vessels and formation of a full 360° fundal wrap around the lower esophagus (21). This pioneering procedure saw an initial success and widespread adaptation, followed by a significant decline due to high complication rates (21,22). Additionally, PPIs were developed in the 1980s and further reduced interest in the open fundoplication procedures (22). For reference, the surgical morbidity rates for anti-reflux procedures were around 12% in the 1980s following introduction of a floppy Nissen procedure in 1977 (23). Thus, only patients who had insufficient symptomatic relief or progressive esophagitis despite optimal medical treatment were considered for traditional open operation (22,23).

A drastic change in the course of surgical management of GERD followed the breakthrough in laparoscopic surgery when the first laparoscopic cholecystectomy was performed in 1987 by Philippe Mouret in Lyon, France (24). In 1991, Dallemagne *et al.* described their initial experience with laparoscopic Nissen fundoplication (LNF) and noted excellent symptom resolution with 0% mortality rate (19-23). Other surgeons found that LARS, which included LNF and partial wraps, resulted in significantly less morbidity and mortality, and shorter recovery period compared to the open approach (22-25). LARS has since become the ideal operation for patients with complications from GERD such as strictures, presence of Barrett's esophagus, esophageal ulceration with bleeding, and those in the younger age group as it may be more cost effective (21,24). Though the initial report by Dallemagne *et al.* demonstrated no mortality, it is important to note that there are serious adverse events (SAE), which may include mortality. Galmiche *et al.* LOTUS trial reported 3% in-hospital morbidity rate and 26.8% SAE overall for the LARS group (26). Additionally, this trial demonstrated that at 5 years dysphagia was noted in 11% of patients ( $P<0.001$ ), bloating in 40% ( $P<0.001$ ) and flatulence in 57% ( $P<0.001$ ) (26).

Historically, complications that have plagued the

**Table 2** Outcomes of fundoplication, magnetic, and endoscopic treatments for GERD

Study (cohort size)	Procedure time (minutes)	Study Length (months)	off PPI % [N]	GERD-HRQL % [N]	Complications
Laparoscopic anti-reflux surgery (LARS)					
Mahon <i>et al.</i> (27) (N=340)	79, range 37–180	12	7.4% PPI dose reduction [8]	GI well-being score improved 31.7 to 37.0 [80]	Esophageal, liver, and splenic injuries, wrap migration
LOTUS Trial (26) (N=554)	n/a	60	90% GERD remission [223]	mean score 6.53±0.85 [204]	Gastric perforation, flatulence, diarrhea
Radiofrequency energy delivery					
Triadafilopoulos <i>et al.</i> (28) (N=118)	Mean 55 [13]	12	30% remained on PPI [27]	65% reduction [60]	Fever, chest pain, dysphagia
Noar <i>et al.</i> (29) (N=217)	Median 25, range 19–45	120	41% off PPI [41]	72% normalization [71]	Bleeding
Transoral incisionless fundoplication (TIF)					
Bell <i>et al.</i> (30) (N=100)	42, range 21–85	6	71% off PPI [27]	75% reduction [64]	Urinary retention, pain
TEMPO Trial (31) (N=63)	38, range 20–68	6	90% off PPI [35]	72% improved [28]	Nausea
Testoni <i>et al.</i> (32) (N=50)	78	12	91.7% reduced PPI [11]	Mean score 9.5±6.1 [12]	Pneumothorax
Magnetic LES Augmentation					
Lipham <i>et al.</i> (33) (N=44)	Median 40, range 19–104	48	15.3% on PPI [20]	100% reduction [23]	Dysphagia, chest pain
Ganz <i>et al.</i> (34) (N=100)	n/a	60	89.4% off PPI [76]	83% [70]	Dysphagia, gas-bloat, regurgitation
Anti-reflux mucosectomy (ARMS)					
Inoue <i>et al.</i> (35) (N=10)	EMR mean 76, range 42–124; ESD 127, range 98–176		100% [10]	n/a	Stricture
Sumi <i>et al.</i> (36) (N=109)	Mean 54.7±27	36	51% [30]	GERDQ score decreased to 6.0±1.9 [21]	Bleeding, perforation

PPI, proton pump inhibitors; GERD-HRQL, gastroesophageal reflux disease related quality of life; GI, gastrointestinal; QOL, quality of life; EMR, Endoscopic mucosal resection, ESD, Endoscopic submucosal dissection.

procedure are the slipped Nissen allowing stomach migration under the wrap, migration into the chest due to non-closure of the crura, breakdown of repair leading to GERD recurrence, and wrap that is too-tight or too-long leading to severe dysphagia (22–25). Thus, while LARS is effective it does have risks and thus warrants a closer look at the multiple trials that have been performed comparing LARS to PPIs (*Table 2*). Additional review of LARS studies is summarized in [Supplementary file 1](#).

### Endoscopic therapies

Endoscopic therapies provide a great alternative for management of GERD. Selection of candidates is crucial as it determines the effectiveness of the procedure. Endoscopic therapy is less invasive and effective for patients with an incomplete response to medical therapy, those who do not prefer long-term medication, or may wish to avoid surgery. Preoperative esophagogastroduodenoscopy (EGD) is necessary to assess the appropriateness for endoscopic therapy. Ideal candidates have a HH  $\leq 2$  cm or Hill grade I or II (37,38). This procedure is offered to patients who have

a contraindication to medical management, who wish to avoid surgery or in whom surgery is contraindicated. Some relative contraindications include body mass index (BMI)  $>35 \text{ kg/m}^2$ , HH  $>5 \text{ cm}$ , portal hypertension, gastroparesis, Barrett's esophagus, pregnancy, and active peptic ulcer disease (30). Additionally, certain patients may be able to qualify for endoscopic management provided their HH is repaired or, if they have gastroparesis or Barrett's, they are on an adequate surveillance and treatment pathway. Few endoscopic therapies have been developed and proven to be effective, we describe four of the most commonly used procedures (Table 2).

### Radiofrequency energy delivery

The Stretta™ (Restech, Houston, TX) procedure involves delivering thermal radiofrequency energy to the LES; however, the exact mechanism is not well understood. One theory is that radiofrequency causes a reduction in the frequency of transient LES relaxations. Other theories propose a decrease in tissue compliance and increase in tensile strength as well as tissue remodeling of the gastro-esophageal junction (GEJ). The system contains a radiofrequency generator and a catheter which contains a balloon basket assembly and four nitinol needle electrodes. The procedure starts with an EGD to locate and measure the distance to the squamocolumnar junction (SCJ). Once located, a guidewire is placed and the Stretta™ catheter is introduced and advanced to 1 cm proximal to the SCJ. The balloon basket is inflated, and the four needle electrodes (22-gauge, 5.5 mm) are introduced into the muscular layer of the GEJ. Energy is released for 60 seconds accompanied by constant water irrigation to prevent thermal injury to the mucosa with resistance continuously measured to ensure effective treatment. After completion, needles are drawn back and the balloon is collapsed. The catheter is turned  $45^\circ$  then the balloon is expanded and the needles are deployed for a total of eight treatments at each level. Energy is delivered at three additional levels: 0.5 cm proximal to the SCJ, at the SCJ, and 0.5 distal to the SCJ. The guidewire is removed, the balloon is distended to 25 mL then pulled back until it is tight to the hiatus, the needles are deployed and energy is applied for another minute. Next, the needles are retracted, balloon deflated and the catheter is rotated  $30^\circ$  for a total of 12 treatments at each level. The final treatment occurs when the balloon is pushed in to the stomach, distended to 22 mL and again retracted until snug. The catheter is removed and an EGD is performed to

evaluate the adequacy of treatments (28,29,39-41).

Safety and efficacy of Stretta™ were analyzed in several studies (Table 2). One open label multicenter study evaluated the outcomes of the Stretta™ procedure in 118 patients with 10 (8.6%) self-limited complications. At 12 months, there was an improvement in the GERD-health-related quality of life scores (GERD-HRQL) score along with decreased acid exposure in the treatment group ( $P=0.0001$ ). Additionally, only 30% of patients required PPIs compared to 88% of patients at baseline ( $P<0.0001$ ) (28).

Longer term results were reported by Noar *et al.* who assessed 217 patients with medically refractory GERD over a 10-year period. After treatment, 41% ( $N=41$ ) of patients entirely stopped the use of PPI while 64% reduced PPI use by half. Moreover, there was 72% improvement in GERD-HRQL. Most common side effects reported were chest discomfort (50%), dyspepsia (25%), and abdominal pain (8.3%) (29).

A meta-analysis conducted by Perry *et al.* included 1,441 subjects from 18 studies and revealed improvement in both GERD-HRQL ( $P=0.001$ ) and acid exposure ( $P=0.007$ ). The most common complications are ulcerative esophagitis and gastroparesis (40). A more recent meta-analysis included 2,468 patients from a total of 28 studies and reported similar results with 49% of patients who required PPIs at baseline required it at follow-up ( $P<0.001$ ). Esophageal acid exposure was reduced by a mean of  $-3.01$  ( $-3.72$ ,  $-2.30$ , random effects model,  $P<0.001$ ) (41).

### TIF

TIF has recently become a popular endoscopic treatment to restore the anti-reflux barrier and treat GERD. This endoscopic fundoplication restores the competency to the LES by deepening the angle of His, accentuating the cardiac notch, supporting the sling fibers, and recreating the flap-valve mechanism. The EsophyX™ device (EndoGastric Solutions, Redmond, WA) is a popular device that is introduced over a flexible endoscope. The endoscope is retroflexed and the lesser curve and greater curve are identified at 12 o'clock and 6 o'clock, respectively. Tissue is rolled and locked on the helical retractor while suction is applied ensuring that the fundus is folded over the esophagus, the stomach is then desufflated. The device is maneuvered into the appropriate position and then "H"-shaped polypropylene fasteners are deployed in order to recreate a new GEJ. Multiple plication sets are placed in anterior, posterior, and longitudinal positions to create a

5 cm long and 300° fundoplication (42). This is similar to LARS as the goal is to create at least 2–4 cm fundoplication with at least 270° rotation.

Numerous studies showed superior outcomes after TIF even out to ten years (Table 2). A multicenter prospective study conducted by Chang *et al.* reported that 80% of patients in the TIF group were completely off PPI therapy at 6 months. In addition, GERD-HRQL was normalized in 73% of TIF patients (42). The TEMPO randomized clinical trial (RCT) compared the efficacy of the TIF procedure (N=40) against maximum dose of PPI therapy (N=23) in patients with GERD. After 6 months, 90% of TIF patients reported cessation of PPIs. Esophageal acid exposure improved in 54% of the TIF group compared to 52% in PPI group (P=0.914). Overall, the TIF procedure was superior to medical therapy in controlling extraesophageal GERD symptoms (31). Another device approved by the Food and Drug Administration (FDA) is the Medigus ultrasonic surgical endostapler (MUSSETM) (Medigusm Omer, Israel). The MUSSETM creates a fundoplication under ultrasound guidance and reported 90% of PPI use halved or ceased at one year (32).

A longer-term study reported reduction in heartburn score, GERD-HRQL, and regurgitation score at 10 years after TIF. Additionally, more than 86.7% of patients stopped or halved their use of PPI medication at 2 years and increased to 91.7% at 10 years (43). More recently, a systematic review and meta-analysis that compared efficacy of LNF *vs.* TIF *vs.* sham or PPI therapy. The TIF was superior in improving GERD-HRQL, while LNF had the highest likelihood of augmenting LES pressure and percent time pH <4 (44).

A major advancement in this technique was combination of HH repair (HHR) with TIF. Janu *et al.* reported their findings of combined HHR and TIF in 99 patients whose HH was 2–5 cm (45). All underwent laparoscopic HHR followed by patient repositioning and TIF and were then evaluated using GERD-HRQL scores which demonstrated increase by 17 points (and no bothersome symptoms) at 12-month follow up. Additionally, they reported no long-term dysphagia or gas-bloat (45).

### **Magnetic LES augmentation**

LINXR reflux management system (Torax Medical, St. Paul, MN) is a series of titanium beads with a magnetic core that strengthens the LES. Patients who are candidates have not had prior gastric surgery, have normal esophageal

function, HH <3 cm, and are not obese (BMI <35 kg/m<sup>2</sup>) (46). Implantation occurs laparoscopically as a tunnel between the esophageal wall and the posterior vagal trunk. The interlinked beads are placed as an alternative to fundoplication and the size is adjusted to fit the esophageal diameter. The device effectively prevents reflux yet opens to a food bolus once peristaltic pressure overcomes the magnetic attraction (46).

Several studies evaluated the safety and efficacy of magnetic sphincter augmentation to treat GERD (Table 2). One multicenter, single-arm study established mean total acid exposure time was reduced 4 years after the LINXR device (P<0.001). Also, GERD-HRQL scores improved in 100% of patients (N=23), while 80% (N=20) stopped taking PPIs. Dysphagia was the most common postoperative complaint and present in 43% of patients (N=20) (46). Similar results were reported by Lipham *et al.* in a study of 100 adults with 89.4% of patients off PPI at 5 years. Complications included “de novo” esophagitis and also dysphagia (33). A review of studies summarized the outcomes from 1000 patients implanted with the sphincter augmentation from 82 institutions across the United States and Europe. Dysphagia and pain were the most frequent postoperative complaints, while there were 0.1% (N=1) perioperative complication, 1.3% (N=14) readmission rate, and 0.1% (N=1) rate of device erosion. Up to 3.4% (N=36) of patients required reoperation for device removal and 5.6% (N=59) required esophageal dilation (34). Another review queried the dataset from the device manufacturers after 9,453 devices were placed between February 2007 to July 2017. In this study, Alicuben *et al.* tallied 29 erosions with the smaller 12-bead device responsible for a 4.93% (N=18) erosion rate (47–49). The majority of eroded devices were first removed endoscopically, followed by laparoscopic removal of the remaining beads. The risk of erosion increased from 0.05% at one year to 0.3% at 4 years (49). This study concluded erosion of the magnetic sphincter augmentation device was rare, successfully managed with minimally invasive techniques, and without long-term sequelae.

It is worth mentioning the Angelchik antireflux device as a historical prosthetic devices placed at the GEJ to treat refractory GERD. The Angelchik prosthesis was a gel-filled silicone C-shaped ring and initially used in 1973 with further description in 1979. The preliminary results were promising with low morbidity and short hospital stay with an estimated 30,000 devices placed. A dense fibrotic scar surrounded the ring and multiple complications began to arise. The most common complication included persistent dysphagia and

was noted in up to 70% patients. In addition, gas-bloat, failure of GERD symptom resolution, ring migration, and erosion occurred. Roughly 15% of patients required removal and the device was ultimately abandoned (48). It is evident the rate of device erosion and the need for subsequent removal is significantly lower in the LINXR group (0.10–0.15%). Furthermore, the LINX device has been associated with a limited inflammatory rind and removal is met with excision of the capsule and modest adhesions (49).

### ARMS

ARMS removes strips of the GEJ mucosa and results in scarring of the cardia with reduction of reflux. The technique was initially described by Inoue *et al.* (35) in a pilot study that involved 10 subjects. The mucosal resection was performed along the lesser curvature via endoscopic mucosal resection (EMR) or submucosal dissection (ESD) in a crescentic fashion as the circumferential technique caused stricture formation in the first two cases. At least a 3cm segment is resected with cap-EMR and snare method or the dual electrocautery knives with the ESD technique. Preservation of the mucosa at the greater curvature, roughly twice the diameter of the endoscope, creates a mucosal flap-valve. Indications for this procedure include refractory GERD, no sliding HH, and patients with short-segment Barrett's esophagus (49). All patients stopped PPI use and the time pH <4 decreased from 29.1% to 3.1%. Circumferential ARMS required multiple balloon dilations to treat stricture formation.

Most recently, a single-center retrospective study evaluated 109 patients with PPI-refractory GERD who underwent ARMS (Table 2). Discontinuation of PPI use was reported in 42% (N=42) of patients at 2 to 6 months and 51% (N=30) at 1 year. There was significant improvement in GERDQ scores as early as 2 months and continued to 1 year after the procedure. In this study, two patients developed postoperative hemorrhage and one had a perforation, all managed endoscopically. Stenosis requiring balloon dilation > 3 times occurred in 14.4% (N=13) patients. Additionally, the authors evidenced limited stenosis when using the "butterfly" technique that protects a small notch of mucosa on the lesser curvature side, between the semicircular segments (35). ARMS was proven to be an effective, minimally invasive, and safe endoscopic treatment for GERD in selected patients (36). However, longer term studies and those involving diverse patient characteristics are needed to

validate this procedure.

### Special population: GERD and obesity

Given the high prevalence of obesity worldwide, it is important to take a closer look at this patient population as the treatment modalities may differ. BMI >30 kg/m<sup>2</sup> is associated with higher odds of GERD (1.94, 1.47 to 2.57) and increased incidence of defective anti-reflux barrier (50,51). Ayazi *et al.* reported a unit increase in BMI was associated with 0.35% increase in total time pH <4 and a 1.46 increase in DeMeester composite score (51). More relevant to this discussion, a BMI >30 kg/m<sup>2</sup> resulted in a 31% symptomatic and physiologic recurrence following LARS. This is compared to 8.0% in patients with BMI 25–29.9 kg/m<sup>2</sup> and only 4.5% in patients with a BMI <25 kg/m<sup>2</sup> (52). The majority of failures were due to wrap disruption rather than intrathoracic wrap migration; suggesting the increased visceral adiposity distorts tissues planes resulting in anatomic failure while the increased intrabdominal pressures breakdown the suture closure and fundoplication.

While it has been shown that weight loss after bariatric surgery consistently improves GERD symptoms however, symptom alleviation differs by type of procedure. The laparoscopic Roux-en-Y gastric bypass (LRYGB) has significant improvement in GERD score 56.5% compared to 46% adjustable gastric band and (41%) laparoscopic sleeve gastrectomy (LSG) (53). GERD resolution was still higher after RYGB (76.9%) compared to biliopancreatic diversion and duodenal switch (BPD/DS) (48.6%) in the super super-obese (BMI >50 kg/m<sup>2</sup>), even though weight loss was superior in the BPD/DS group (54). The Swiss Multicenter Bypass or Sleeve Study (SM-BOSS) is an RCT that demonstrated that the remission of GERD was higher after RYGB at 60.4% compared to 25% for LSG at 5 years. Also, GERD symptoms increased after LSG to 31.8% compared with 6.3% in LRYGB (55). "De novo" reflux was reported in 22.9% (N=60) of patients after LSG compared to 0% in LSG plus HHR (56). It is important to note that HHR was not controlled in these studies and could significantly contribute to the outcomes. The current American Society for Metabolic and Bariatric Surgery (ASMBS) generated a care pathway for LSG that lists selective use of EGD, UGI, and pH/manometry (57). Others advocate for including these studies as routine preoperative workup for patients with suspected or known GERD (56,58). Generous dissection of the hiatus with and liberal repair of HH is routinely recommended for LSG

patients though (56,57).

## Conclusions

GERD is a common ailment in Western population with a variety of treatment modalities available. While PPIs remain the first line treatment, it is important to realize that therapy should be individualized and factors such as patient preference, symptom severity as well as presence of anatomic abnormalities should be considered in order to find the most effective therapy. Given the low risk profile, newer GERD treatment modalities including endoscopic and magnetic therapies have shown promising results and thus, more research is needed to study the long-term outcomes.

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## References

1. Dunlap JJ, Patterson S. Gastroesophageal reflux disease. *Gastroenterol Nurs* 2019;42:185-8.
2. Ho KY, Kang JY. Reflux esophagitis patients in Singapore have motor and acid exposure abnormalities similar to patients in the Western hemisphere. *Am J Gastroenterol* 1999;94:1186-91.
3. Friedenberg FK, Hanlon A, Vanar V, et al. Trends in gastroesophageal reflux disease as measured by the National Ambulatory Medical Care Survey. *Digest Dis Sci* 2010;55:1911-7.
4. Nau P, Jackson HT, Aryaie A, et al. Surgical management of gastroesophageal reflux disease in the obese patient. *Surg Endosc* 2020;34:450-7.
5. Wileman SM, McCann S, Grant AM, et al. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database Syst Rev* 2010;(3):CD003243.
6. Nabi Z, Reddy DN. Endoscopic management of gastroesophageal reflux disease: revisited. *Clin Endosc* 2016;49:408-16.
7. Tack J, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. *Gastroenterology* 2018;154:277-88.
8. Xie C, Li Y, Zhang N, et al. Gastroesophageal flap valve reflected EGJ morphology and correlated to acid reflux. *BMC Gastroenterol* 2017;17:118.
9. Lee YY, McColl KEL. Pathophysiology of gastroesophageal reflux disease. *Best Pract Res Clin Gastroenterol* 2013;27:339-51.
10. Gyawali CP, Kahliras PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon consensus. *Gut* 2018;67:1351-62.
11. Katkhouda, N. Laparoscopic treatment of gastroesophageal reflux disease—defining a gold standard. *Surg Endosc* 1995;9:765-7.
12. Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the esophageal diagnostic advisory panel. *J Am Coll Surg* 2013;217:586-97.
13. Patti MG. An Evidence-Based Approach to the Treatment of Gastroesophageal Reflux Disease. *JAMA Surg* 2016;151:73-8.
14. Johnson LF, Demeester TR. Twenty-four-hour pH



- monitoring of the distal esophagus. A quantitative measure of the distal esophagus. *Am J Gastroenterol* 1974;62:325-32.
15. Labenz J, Malfertheiner P. Treatment of uncomplicated reflux disease. *World J Gastroenterol* 2005;11(28):4291-99.
  16. Kethman W, Hawn M. New approaches to gastroesophageal reflux disease. *J Gastrointest Surg* 2017;21:1544-52.
  17. Vela MF. Medical treatments of GERD: the old and new. *Gastroenterol Clin North Am* 2014;43:121-33.
  18. Lee L, Ramos-Alvarez I, Ito T, et al. Insights into effects/risks of chronic hypergastrinemia and lifelong PPI treatment in man based on studies of patients with Zollinger-Ellison syndrome. *Int J Mol Sci* 2019;20:5128.
  19. Brusselaers N, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of esophageal cancer. *Cancer Epidemiol* 2018;53:172-77.
  20. Schein M, Schein H, Wise L. Rudolf Nissen: the man behind the fundoplication. *Surgery* 1999;125:347-53.
  21. Nissen R. Eine einfache Operation zur Beeinflussung der Refluxesophagitis [A simple operation for control of reflux esophagitis]. *Schweiz Med Wochenschr* 1956;86:590-2.
  22. Bammer T, Hinder R, Klaus A, et al. Five- to eight-year outcome of the first laparoscopic Nissen funduplications. *J Gastrointest Surg* 2001;5:42-8.
  23. Dallemagne B, Weerts JM, Jehaes C, et al. Laparoscopic Nissen fundoplication: preliminary report. *Surg Laparosc Endosc* 1991;1:138-43.
  24. Blum CA, Adams DB. Who did the first laparoscopic cholecystectomy. *J Minim Access Surg* 2011;7:165-8.
  25. Lin DC, Chun CL, Triadafilopoulos G. Evaluation and management of patients with symptoms after anti-reflux surgery. *Dis Esophagus* 2015;28:1-10.
  26. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 2011;305:1969-77.
  27. Mahon D, Rhodes M, Decadt B, et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastroesophageal reflux. *Br J Surg* 2005;92:695-9.
  28. Triadafilopoulos G, DiBaise J, Nostrant TT, et al. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. *Gastrointest Endosc* 2002;55:149-56.
  29. Noar M, Squires P, Noar E, et al. Long-term maintenance effect of radiofrequency energy delivery for refractory GERD: a decade later. *Surg Endosc* 2014;28:2323-33.
  30. Bell RC, Mavrelis PG, Barnes WE, et al. A prospective multicenter registry of patients with chronic gastroesophageal reflux disease receiving transoral incisionless fundoplication. *J Am Coll Surg* 2012;215:794-809.
  31. Trad KS, Barnes WE, Simoni G, et al. Transoral incisionless fundoplication effective in eliminating GERD symptoms in partial responders to proton pump inhibitor therapy at 6 months: the TEMPO Randomized Clinical Trial. *Surg Innov* 2015;22:26-40.
  32. Testoni PA, Testoni S, Mazzoleni G, et al. Transoral incisionless fundoplication with an ultrasonic surgical endostapler for the treatment of gastroesophageal reflux disease: 12-month outcomes. *Endoscopy* 2020;52:469-73.
  33. Lipham JC, DeMeester TR, Ganz RA, et al. The LINX® reflux management system: confirmed safety and efficacy now at 4 years. *Surg Endosc* 2012;26:2944-9.
  34. Ganz RA, Edmundowics SA, Taiganides PA, et al. Long-term Outcomes of Patients Receiving a Magnetic Sphincter Augmentation Device for Gastroesophageal Reflux. *Clin Gastroenterol Hepatol* 2016;14:671-7.
  35. Inoue H, Ito H, Ikeda H, et al. Anti-reflux mucosectomy for gastroesophageal reflux disease in the absence of hiatus hernia: a pilot study. *Ann Gastroenterol* 2014;27:346-51.
  36. Sumi K, Inoue H, Kobayashi Y, et al. Endoscopic treatment of proton pump inhibitor-refractory gastroesophageal reflux disease with anti-reflux mucosectomy: experience of 109 cases. *Dig Endosc* 2020. [Epub ahead of print]. doi: 10.1111/den.13727.
  37. Yeh RW, Triadafilopoulos. Endoscopic antireflux therapy: the Stretta procedure. *Thorac Surg Clin* 2005;15:395-403.
  38. Leeds S, Reavis K. Endoluminal therapies for gastroesophageal reflux disease. *Gastrointest Endosc Clin N Am* 2013;23:41-51.
  39. Sowa P, Samarasena JB. Nonablative Radiofrequency Treatment for Gastroesophageal Reflux Disease (STRETTA). *Gastrointest Endosc Clin N Am* 2020;30:253-65.
  40. Perry KA, Banerjee A, Melvin WS. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2012;22:283-8.
  41. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. *Surg Endosc*

- 2017;31:4865-82.
42. Chang KJ, Bell R. Transoral Incisionless Fundoplication. *Gastrointest Endosc Clin N Am* 2020;30:267-89.
  43. Testoni PA, Testoni A, Distefano G, et al. Transoral incisionless fundoplication with EsophyX for gastroesophageal reflux disease: clinical efficacy is maintained up to 10 years. *Endosc Int Open* 2019;7:E647-54.
  44. Richter JE, Kumar A, Lipka S, et al. Efficacy of Laparoscopic Nissen Fundoplication vs Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. *Gastroenterology* 2018;154:1298-308.e7.
  45. Janu P, Shughoury AB, Venkat K, et al. Laparoscopic hiatal hernia repair followed by transoral incisionless fundoplication with EsophyX device (HH + TIF): efficacy and safety in two community hospitals. *Surg Innov* 2019;26:675-86.
  46. Kuckelman JP, Barron MR, Martin MJ. "The missing LINX" for gastroesophageal reflux disease: Operative techniques video for the Linx magnetic sphincter augmentation procedure. *Am J Surg* 2017;213:984-87.
  47. Lipham JC, Taiganides PA, Louie BE, et al. Safety analysis of first 1000 patients treated with magnetic sphincter augmentation for gastroesophageal reflux disease. *Dis Esophagus* 2015;28:305-11.
  48. Varshney S, Kelly JJ, Branagan G, et al. Angelchick prosthesis revisited. *World J Surg* 2002;26:129-33.
  49. Alicuben ET, Bell RCW, Jobe BA, et al. Worldwide experience with erosion of the magnetic sphincter augmentation device. *J Gastrointest Surg* 2018;22:1442-47.
  50. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143:199-211.
  51. Ayazi S, Hagen JA, Chan LS, et al. Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. *J Gastrointest Surg* 2009;13:1440-7.
  52. Perez AR, Moncure AC, Rattner DW. Obesity is a major cause of failure for both abdominal and transthoracic antireflux operations. *Gastroenterology* 1999;116: A1343.
  53. Pallati PK, Shaligram A, Shostrom VK, et al. Improvement in gastroesophageal reflux disease symptoms after various bariatric procedures: review of the Bariatric Outcomes Longitudinal Database. *Surg Obes Relat Dis* 2014;10:502-7.
  54. Prachand VN, Ward M, ALverdy JC. Duodenal switch provides superior resolution of metabolic comorbidities independent of weight loss in the super-obese (BMI $\geq$ 50 kg/m<sup>2</sup>) compared with gastric bypass. *J Gastrointest Surg* 2010;14:211-20.
  55. Peterli R, Wolnerhanssen BK, Peters T, et al. Effect of Laparoscopic Sleeve Gastrectomy vs Laparoscopic Roux-en-Y Gastric Bypass on Weight Loss in Patients With Morbid Obesity: The SM-BOSS Randomized Clinical Trial. *JAMA* 2018;319:255-65.
  56. Soricelli E, Iossa A, Casella G, et al. Sleeve gastrectomy and crural repair in obese patients with gastroesophageal reflux disease and/or hiatal hernia. *Surg Obes Relat Dis* 2013;9:356-61.
  57. Telem DA, Gould J, Pesta C, et al. American society of metabolic and bariatric surgery: care pathway for laparoscopic sleeve gastrectomy. *Surg Obes Relat Dis* 2017;13:742-9.
  58. Rebecchi F, Allaix ME, Giaccone C, et al. Gastroesophageal reflux disease and laparoscopic sleeve gastrectomy: a physiopathologic evaluation. *Ann Surg* 2014;260:909-14.

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## Detailed review of LARS studies

### *Mahon et al. 2005 (58)*

This was an early PPI *vs.* LARS RCT in which a total of 217 patients were randomized to optimal medical therapy with PPIs (108 patients) or to LNF (109 patients) with preoperative age, weight, and the severity of reflux symptoms similar in both groups. After 3 months, the LNF group reported mean DeMeester scores significantly lower than the PPI group (8.6 versus 17.7;  $P < 0.001$ ). Additionally, general well-being improved in both groups at 3 months and 1 year using Psychological General Well-Being Index and Gastrointestinal Symptom Rating Scale. PPI dose escalation occurred in 15 (13.9%) in the PPI group. In the LNF group, there 4 (3.7%) major intraoperative complications and 5 (4.6%) patients developed dysphagia that remained for more than 3 months after surgery.

### *LOTUS Trial, Galimiche et al. 2011 (26)*

The LOTUS trial study compared the effects of esomeprazole *vs.* LARS in 372 patients with chronic GERD. At 5 years, 85% patients in the LARS group remained in remission compared with 92% of patients in the medically treated group ( $P = 0.25$ ). An increased dose of PPI was required to control symptoms by 23% in the medical arm while the LARS group reported bloating and flatulence. Prevalence and severity of acid regurgitation and dysphagia showed greater improvement in the LARS than in the medical group ( $P < 0.001$ ).

SAEs were found in 28.6% of the LARS group and 24.1% of PPI group. Overall LARS and continuous PPI treatment were similarly effective and well-tolerated therapeutic strategies for providing effective control of GERD for 5 years.

## References

1. Mahon D, Rhodes M, Decadt B et al. Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton pump inhibitors for treatment of chronic gastro-oesophageal reflux. *Br J Surg* 2005;92:695-9.