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# Advances in Endoscopic Management of GERD: A Brief Review on TIF Procedure

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is arguably the commonest gastrointestinal (GI) pathology encountered by gastroenterologists, and primary care physicians, with prevalence reported to be up to 27.8% in the North America.[1] GERD greatly impacts quality of life due to missed work days and leisure activities,[2] and resultant increase in health-care costs with frequent clinic visits, diagnostic testing and medication use.

Lifestyle and dietary modifications are highly recommended as initial management strategy for GERD symptoms.[3] Recommendations include exercise and weight loss for obese/overweight individuals, cessation of smoking and alcohol use, elevation of head-end of bed to 30 degrees, eliminating late night meals and avoiding trigger foods.[4] Such modifications have physiologic effects on the GI tract, including decreased pressure on the gastroesophageal junction (GEJ)[5] and normalization of lower esophageal sphincter (LES) pressure.[6] First-line medical management of GERD is an eight-week trial of proton-pump inhibitor (PPI) therapy. In PPI non-responders or patients with "troublesome" dysphagia, the American Gastroenterological Association (AGA) recommends early endoscopic evaluation with biopsies for further assessment.[7]

Since medical therapy only alters the pH of the gastric refluxate, GERD may persist despite

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optimized medical therapy. Historically, surgical fundoplication and bariatric surgery, specifically the Roux-en-Y technique were the most common approaches to mitigate this issue. Surgery is usually reserved for those with desire for medication discontinuation, esophagitis persistent despite optimal therapy and structural abnormalities such as hiatal hernia.[8] Surgery is predictably offered to patients with typical symptoms, who demonstrate abnormal esophageal pH, as evidence suggests that these patients are more likely to have resolution of their symptoms.[9] Complications of traditional surgical Nissen fundoplication, as well as newer partial fundoplications, include dysphagia and gas-bloat syndrome.[10] Regurgitation and heartburn have been noted to recur in up to 29% and 35% of patients, respectively, after 10 years.[11-12]

In the last few years, new innovations in the field of endoscopy have resulted in several endoscopic strategies attempting to bridge the gap between medical (PPI) and surgical (Nissen and others) management of chronic GERD. The three procedures approved by the Food and Drug Administration (FDA) include Stretta, which delivers thermal energy to multiple sites in the LES and gastric cardia, producing a tissue-tightening effect related to heat-induced fibrosis, MUSE (Medigus Ultrasonic Surgical Endostapler), which uses 5 standard surgical staples (instead of fasteners) in 3 staggered rows to attach the gastric fundus to the esophagus, creating an anterior partial fundoplication, and TIF (Transoral Incisionless Fundoplication), which is anatomically and functionally similar to fundoplication, wherein the gastric fundus is folded up and around the distal esophagus and anchored with polypropylene fasteners. TIF targets the main anatomical mechanism involved in the pathophysiology of GERD, by reconstructing the GE valve (GEV). The goal of TIF procedure is to create a true flap valve around the GEJ by creating a 270-degree endoscopic fundoplication,[13] and has shown favorable outcomes with low rates of adverse events, thus providing hope to poor surgical candidates.

## Patient Selection for TIF Procedure

There are two commonly practiced approaches for endoscopic assessment of anti-reflux barrier of the GEJ; one by measuring the axial length of the hiatal hernia,[14] and second by assessing the GE flap valve graded by the Hill classification, on a scale of I–IV, with higher value reflecting more severe disruption of the GEJ and less LES pressure.[15] The endoscopic measurement of axial length of hiatal hernia can be less accurate due to effects of breathing and the physiological dynamics in the area,[16] and for this reason, Hill approach is considered better and more accurate.

Traditionally, the presence of typical GERD symptoms and a positive response to PPI therapy increase the chances of superior outcomes following anti-reflux surgery.[17] However, ~ 60% GERD patients report satisfaction with lifestyle modifications and/or medical therapy, and those with inadequate response and poor quality of life typically seek alternative treatment plans, including TIF. Conversely, for both typical and atypical symptoms of GERD, elevated pre-operative GERD health-related quality of life (GERD-HRQL) score on PPI was found to be a predictor of successful outcome of TIF in patients with persistent symptoms despite medical therapy.[18] This conundrum forms the pivotal challenge in appropriate patient selection.

Similar to the workup for surgical approach (Nissen fundoplication), pre-TIF assessment to support objective evidence of GERD must include pH impedance testing (i.e. pathologic acid reflux on ambulatory pH monitoring in the upright and supine positions), esophageal manometry (i.e. exclusion of motility disorders) and esophagogastroduodenoscopy (EGD) (i.e. mild Los Angeles Class A or B esophagitis).[19] Excellent outcomes were reported in a prospective, randomized, multicenter TEMPO (TIF EsophyX vs Medical PPI Open Label) study when TIF was performed on GERD patients with Hill grades I/II anatomy and effective esophageal motility.[19-20] In this study, patients with severe erosive esophagitis (Los Angeles grade C or D), and hiatal hernias with Hill Grade > II were excluded. Moreover, lower success rates were reported in the RESPECT (Randomized EsophyX® vs. Sham/Placebo Controlled Trial) trial, when patients with Hill grade III/IV hiatal hernias were included.[21] Therefore, an optimal TIF candidate is one with chronic GERD with partial or complete symptom

control on PPI therapy, and minimal anatomical distortion of the GEJ (absent or < 2 cm hiatal hernia or Hill grades I/II) and preserved motility. With appropriate patient selection, TIF can fill the "therapeutic gap" that exists between PPI and surgical options (laparoscopic fundoplication).

The TIF procedure might not be an ideal option for those with abnormal anatomy, which would prohibit the insertion and safe advancement of the EsophyX device, such as the presence of esophageal stricture/stenosis, esophageal diverticula or paraesophageal hernia. The procedure is also not advised for patients with bleeding disorders or esophageal varices, due to high risk of bleeding. Furthermore, patients with esophageal dysmotility, large hiatal hernias (> 2 cm) with Hill grade III-IV (if cannot be surgically repaired), active esophageal infection (fungal or bacterial) or inflammation (severe esophagitis), morbid obesity (BMI > 35), limited neck mobility and cardiopulmonary or other contraindications for endoscopy and/or general anesthesia should be excluded.

## Evolution of TIF Procedure

The TIF procedure currently performed in the United States is a result of several years of evolution and development. The original iteration of this procedure was known as endoluminal fundoplication (ELF), first performed in 2005 in Europe, and within 2 years it was cleared to be used in the United States by the Food and Drug Administration (FDA).[22-23] ELF involved a fundus-to-fundus fundoplication, with all fasteners deployed below the Z-line, to allow reduction of small hiatal hernia while fashioning longitudinal gastro-gastric plication, without creating a wrap.[24] ELF paved path for the next generation of procedure (TIF 1.0), which allowed esophago-gastric fundoplication around the GEJ using the EsophyX device (EndoGastric Solutions, Redmond, WA, USA), wherein the fasteners were placed up to 1 cm above the Z line (just proximal to the GE junction), but again, a wrap was not performed.[24] This technique underwent several refinements to reach its current format (TIF 2.0) which uses the EsophyX Z device (launched in 2017) to successfully replicate the principles and outcomes of traditional surgical fundoplication. TIF 2.0 combines partial fundoplication around the distal esophagus with fashioning a rotational wrap of the cardia and fundus circumferentially around the distal esophagus, and the fasteners are placed 1-3 cm above the Z-line.[23]

## Description of TIF 2.0 Procedure[25]

The TIF 2.0 procedure ideally requires 2 operators; one to control the gastroscope and provide visualization, while the second to control the EsophyX Z device.

The procedure is performed under general anesthesia, with usage of a paralytic agent to induce muscle relaxation to minimize intra-operative diaphragmatic sliding movements. Also, mechanical ventilation with application of positive end-expiratory pressure (PEEP) is important to separate the diaphragmatic surface, which facilitates plication. Supine patient position is often favored to decrease liver pressure on the GE junction, and carbon dioxide ($CO_2$) insufflation is preferred over air given less patient discomfort and safer profile in case of perforation.

Steps of TIF 2.0 procedure include:

(i) A pre-TIF EGD is performed to carefully examine the esophagus, stomach and duodenum, confirm the established diagnosis, and also document the anatomical landmarks including Z-line, diaphragmatic impingement and hiatal hernia (axial length and Hill grade) (Figure 1A.).

(ii) The EsophyX Z device is prepared for use by lubricating the channels of the device with mineral oil and lubricating the external parts of the device with water-soluble lubricant.

(iii) The gastroscope is inserted through the central channel of the EsophyX Z device, and the platform is then gently glided through the patient mouth into the stomach under constant visualization (Figure 1B.).

(iv) The tissue mold is closed and the scope is advanced 10-15 cm beyond the tissue mold and retroflexed to allow visualization of the GEJ throughout the procedure.

(v) GEV reconstruction starts with engagement of helical retractor into the tissue slightly distal to

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*(continued from page 26)*

the Z-line, and then using the tissue mold of the device, the gastric fundus is circumferentially folded around the distal esophagus. All tissue-manipulating elements are then locked.

(vi) An integrated suction apparatus is activated to gently grasp the distal esophagus to position it in the abdominal cavity, distal to the diaphragm, as the EsophyX Z device is rotated to wrap the gastric fundus toward the lesser curvature of the stomach. Subsequently, two H-Shaped non-absorbable fasteners are deployed above the GEJ, through apposed layers of esophageal and fundus tissue to anchor the repair (Figure 1C.)

(vii) The EsophyX Z device is rotated on its long axis and this sequence (retract, wrap and appose) is repeated to implant approximately 20 fasteners to create fusion of the esophageal and fundus tissues to create the final product, which is a full thickness, omega shaped, partial circumferential (270-degree wrap) gastro-esophageal fundoplication (Figure 1D.).

## OUTCOMES OF TIF PROCEDURE

### (a) GERD symptoms and HRQL improvement

Resolution of typical GERD symptoms, such as heartburn and regurgitation, appears to be sustained after TIF in long-term follow-up studies. Normalization of reflux symptoms index scores has been reported in 73% in 6 months and 65% in 2-year follow-up.[26-27]

Two key long-term clinical studies evaluating the efficacy of TIF in the United States are TEMPO and RESPECT trials. In TEMPO trial (cross over trial between incomplete responders to PPI therapy and TIF 2.0 therapy), complete elimination of regurgitation was reported in 65% patients at 6 months, 87% at 3 years and 86% at 5 years.[28-29] In comparison, RESPECT trial (TIF 2.0 versus a sham procedure with PPI therapy), 67% had improvement of regurgitation in 6 months and 72% remained asymptomatic in 12 months.[21]

Multiple meta-analyses,[30-31] with pooled estimates from over 1000 patients, demonstrate a statistically significant improvement in GERD-HRQL after TIF procedure (mean difference = 17.72; 95%CI: 17.31-18.14). A recent meta-analysis by Huang et al. abstracted from 13

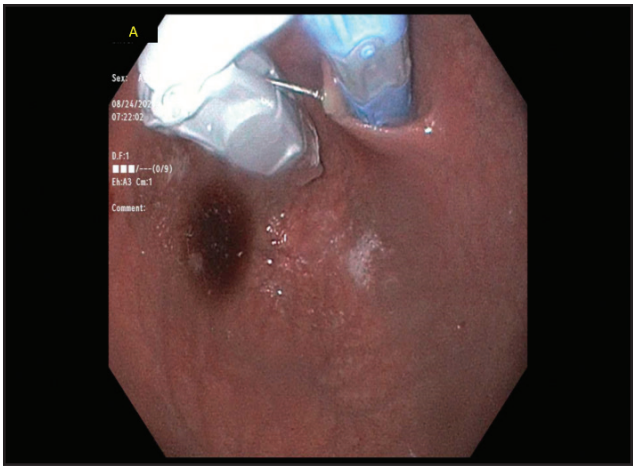


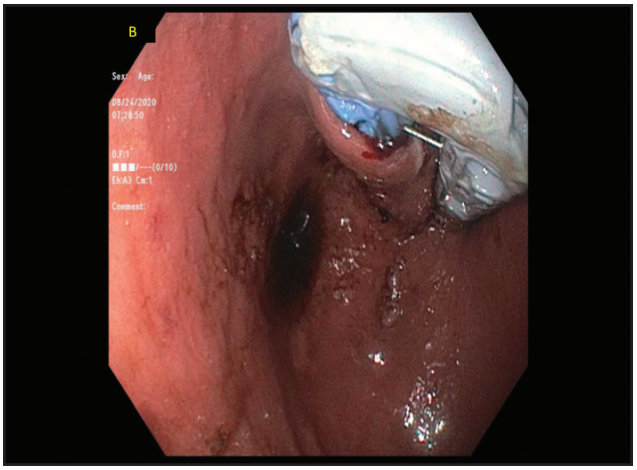
**Figure 1A. After Pre-TIF EGD to document anatomical landmarks (Z-line, diaphragmatic impingement and axial length & Hill grade of hiatal hernia) followed by positioning of EsophyX Z device in retroflexion and tissue mold is closed.** *Images courtesy of Dr. Amy Tyberg, Rutgers Robert Wood Johnson University Hospital, New Jersey, USA*

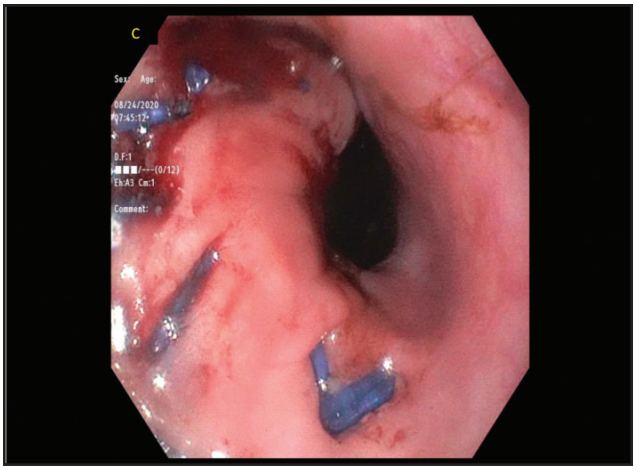
prospective studies and 5 randomized control trials was remarkable for a decreased total number of reflux episodes, without reported gas-bloat symptoms after TIF compared to the PPI/sham groups.[32] Passaretti et al. extended the follow-up to 10 years, and showed persistence of improved mean GERD-HRQL scores after TIF.[33]

Based on the current literature, TIF offers promising results for long-term symptomatic control in patients with typical GERD symptoms and presence of < 2 cm Hill grade I-II hiatal hernia. Additionally, TEMPO trial was also remarkable for improvement of atypical GERD symptoms, such as hoarseness, throat clearing, excess throat mucus, dysphagia, and cough in 80% of patients at 5-year follow-up.[29] Based on these results, the TIF procedure appears to be a valuable alternative for well-selected patients with significant atypical symptoms.

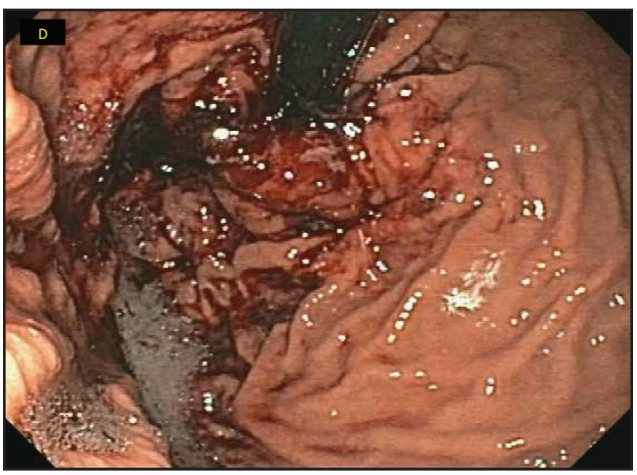
### (b) Anti-secretory (PPI) Medication Cessation

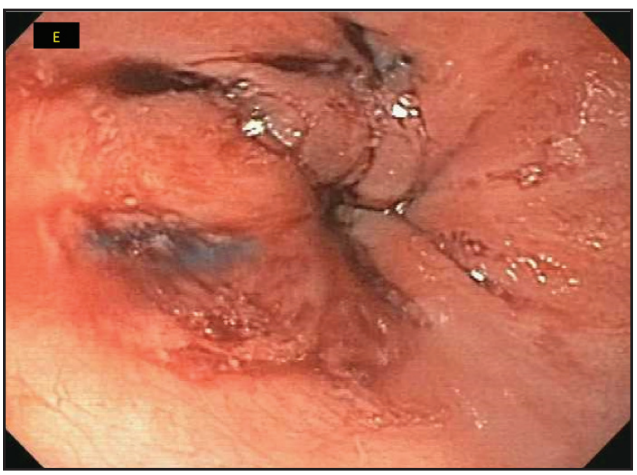
PPI cessation is considered a robust measure of symptom and quality of life (QoL) improvement in patients with chronic GERD. Complete cessation of PPIs was reported in up to 71% patients in 3 years and 46% patients 5 years after TIF in the TEMPO trail,[28-29] and similar trends were observed




**Figures 1B. and 1C. GE valve reconstruction with engagement of helical retractor to fold the gastric fundus around the distal esophagus and application of fasteners.**
*Images courtesy of Dr. Amy Tyberg, Rutgers Robert Wood Johnson University Hospital, New Jersey, USA*




**Figures 1D. and 1E. Full thickness 270-degree gastro-esophageal fundoplication achieved (retroflexed and forward views).**
*Images courtesy of Dr. Amy Tyberg, Rutgers Robert Wood Johnson University Hospital, New Jersey, USA*

in the RESPECT trial as well.[21] Ten year follow-up data from a separate cohort was equally reassuring, with rates of patients who successfully stopped or halved anti-secretive therapy 2, 3, 5, 7, and 10 years after the TIF procedure being 86.7 %, 84.4 %, 73.5 %, 83.3 %, and 91.7 %, respectively.[33] Similarly, patients remained in clinical remission off anti-secretory therapy for significantly longer period of time after TIF (60% at 6 months), when compared to sham procedure.[27]

## (c) Objective Physiological Outcomes

TIF has been shown to achieve normalization of acid exposure in the distal esophagus in up to 69%[35] in European studies,[34] and 57% in the United States TIF registry.[27] TIF also heals esophagitis in between 77-100% of patients, which is arguably a more clinically relevant metric.[21,29] However, along the lines of previous observations evaluating GERD therapies,[35-37] recent TIF studies confirm a poor correlation between post-TIF symptom control and pH normalization.[19,21]

In addition, TIF is thought to decrease the number of postprandial transient LES relaxation (TLESR) episodes, resulting in significant reduction in the GEJ distensibility.[38] It also selectively

reduces liquid-containing reflux episodes, whereas gas reflux events remain unaffected. This accounts for gas ventilation following the TIF procedure while avoiding gas bloat symptom commonly accompanying laparoscopic Nissen fundoplication.

## (d) Durability

Different iterations of TIF have been successfully performed over a decade now, with constant improvisations in its technique and equipment. In literature, TIF failures have been defined as persistent GERD symptoms or worsening GERD-HRQL scores. Previous per-oral incisionless fundoplication techniques (ELF and TIF 1.0, both of which created plication without a wrap) reported higher failure rate (~ 36%)39-40, with 5% re-operation rate in the TEMPO trial,[29] which is comparable to 5-6% re-operation rates of surgical fundoplication.[41] This occurred for a variety of reasons, including lack of wrap around the plication, device malfunction at implantation and persistent symptoms due to hiatal hernia or displaced TIF valve.[29] TEMPO and RESPECT trials in the US,[21,28-29] and randomized sham trial in Europe33 have provided long-term (5 and 10 year) durability data on TIF 2.0, and supported non-significant change in symptom control over time.

## (E) Safety and Adverse Events and Post-Operative Care

Across all studies, a 2.4% complication rate for TIF has been reported.[32] The most common reported complications include perforation, bleeding, pleural effusion and dysphagia.[32] Mortality directly related to TIF procedure is extremely uncommon, with only one reported death till date.[42] Traditional anti-reflux surgeries have higher incidence of post-operative dysphagia, bloating and excess flatulence in comparison to TIF procedure. In fact, preexisting dysphagia, gas bloat, and flatulence reportedly improved after TIF.[29] Although, minor adverse events such as post-operative nausea and abdominal discomfort are common after TIF, major adverse events such as pleural effusion, mediastinitis, abscess, and esophageal perforation are possible.[43-44]

## (f) Treatment Failure and Surgical Revision

Similar to surgical fundoplication, treatment failure and recurrent symptoms after TIF procedure have been reported, with up to 5-18% patients requiring surgical revision after TIF failure.[29,45-46] In TEMPO 5-year follow-up, surgical revision was required in 5% after the initial TIF procedure.[29] However, post-TIF failure surgical revision is challenging. In order to safely perform Nissen fundoplication, the TIF wrap needs to be freed by cutting the fasteners, however due to scar tissue and adhesions, surgery carries higher risk of complications especially gastric wall injuries such as perforation, bleeding, abscess formation. Furnée et al. reported 27% gastric perforation during surgical revision after failed TIF procedure,[45] which is higher than 13% reported gastric perforation after Nissen revision[47] and 2% observed gastric perforation during primary anti-reflux surgery.[48-49] Furthermore, incidence of dysphagia in post-TIF surgical revision patients appears high.[45]

Patients with hiatal hernia > 2 cm were excluded from the TEMPO clinical trial.[29] Testoni et al. included patients with any Hill grade or hiatal hernia size in their 6-year trial, and noted that patients with Hill grade II-IV or hiatal hernia > 2cm had less favorable response at 12 months.[50] Number of fasteners released also has been reported as an independent factor in predicting optimal outcome after the TIF procedure.[50] [Testoni et al.; responders vs non-responders: ($10 \pm 2$ vs. $14 \pm 2$; $p = 0.01$)]. Furthermore, Rabach et al. postulated that anatomic structures around the GE junction such as the phreno-esophageal ligament and esophageal fat pad are not amenable to endoscopic correction, resulting in long term TIF failure.[51] Moreover, Bell et al. noted hiatal hernia recurrence, disrupted wrap, traction and adhesion from the fasteners during revision laparoscopic anti-reflux surgery, thereby explaining TIF failure.[52]

## (g) Cost and Coverage

For years TIF was considered an experimental option in lieu of surgical approach, and hence not covered by Medicare/Medicaid or commercial insurances, requiring patients to pay ballpark of the cost out of pocket. As TIF procedure evolved over years, with establishment of its efficacy and long term beneficial effects through clinical trials, the Centers of Medicare and Medicaid Services

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(CMS) announced on January 1, 2018 coverage of TIF 2.0 procedure with the EsophyX device at all Medicare Administrative Contractors.[53] More commercial insurers followed the lead to support reimbursing TIF procedure. Despite having a universal CPT code (43210) and increasing support from CMS and other private insurers, a great deal of communication and written approval requests is usually required before scheduling the procedure.[53]

## Post-operative Care after TIF Procedure

In most centers, patients are admitted in the hospital for a short observation after TIF procedure, with care emphasizing on control of sub-sternal discomfort/pain and aggressive management of nausea to prevent disruption of plication with vomiting/retching. Additionally, patients are monitored for bleeding or any delayed cardiopulmonary complications or post-procedure infections/leaks. If patient develops any leukocytosis or features of systemic inflammatory response syndrome (SIRS) like tachycardia, fever, tachypnea, contrast studies (gastrografin based) are performed to investigate a possible leak. If immediate post-operative course is uneventful, then patient is placed on a stepwise dietary plan, entailing a 2 week full liquid diet, 1 week puree diet, 1 week soft diet followed by modified regular diet avoiding hard dried food, and finally regular diet in the 6$^{th}$ week. This graduated regimen is believed to promote optimal healing response by improving esophageal muscular strength and peristaltic coordination in the postoperative period.

## Combined TIF and Laparoscopic Hiatal Hernia Repair (LHHR)

Patients with hiatal hernias > 2 cm may become candidates for TIF if the hernia can be reduced to ≤ 2 cm. Clinical data extrapolated from existing studies have demonstrated that concomitant LHHR immediately followed by TIF 2.0 procedure is safe and effective in patients requiring repair of both anatomical defects.[21,28-29,33-34] Although comprehensive literature on this combined (TIF+LHHR) approach is still evolving, but, in available studies, it appears to have similar symptom control and normalization of esophageal pH, without the gas-bloat syndrome that deterred patients from undergoing anatomic repair in the past.[43,54]



## TIF versus Laparoscopic Nissen Fundoplication (LNF)

Current data is lacking a parallel long-term controlled clinical trial evaluating the utility and response to TIF versus LNF. Most recently Richter et al. published a systematic review and network meta-analysis to summarize the efficacy of TIF vs LNF vs PPI use. GERD-HRQL were noted to be higher in TIF recipients, however patients with LNF procedure had higher LES pressure (0.78 vs 0.72) and decreased percent time pH <4 in long-term (0.99 vs 0.32).[55]

## Laparoscopic Magnetic Sphincter Augmentation (LINX)

Another minimally invasive procedure that has shown promising result is laparoscopic magnetic sphincter augmentation, also know as the LINX procedure. The device was approved by the FDA in 2012, and consists of an expandable dynamic ring of magnetic beads, which increases the length and pressure of the esophagogastric junction. Patients with LA class A or B esophagitis are the best candidates for LINX procedure; in contrary, any size hiatal hernia requires repair before the LINX procedure. The least favorable candidates for the LINX procedure are those with gastroparesis, prior upper abdominal surgeries, metal allergies or presence of pacemaker or defibrillator.[51] Similar to TIF, LINX procedure has also shown promising result in improvement of GERD-HRQL to 3.3-6 post procedure.[56-60] Acid exposure improvement after LINX has been reported between 50-80%. PPI secession reported to be achieved in 72-85.3% of patients in long term studies.[56-60] In comparison to TIF, LINX procedure has higher side effect profile; dysphagia has been reported in up to 70% of cases, regurgitation in 50% as well as inability to belch. To date, there is no prospective controlled trial comparing efficacy of LINX procedure with TIF procedure.

## CONCLUSION

To summarize, TIF is a minimally invasive incisionless endoscopic procedure, which has demonstrated promising outcome in long-term symptomatic management of chronic GERD, with a shorter recovery time and superior safety profile compared to surgical equivalent options. With over 22,000 TIF 2.0 procedures performed worldwide using the latest iteration of EsophyX Z device, along with coverage benefit for all Medicare beneficiaries throughout the United States (using CPT code 43210 EGD esophago-gastric fundoplasty + APC 5331 Complex GI procedures), and increasing support from other insurance carriers, TIF 2.0 appears to be well positioned to fill the 'therapy gap' between medical treatments (PPI) and invasive surgical procedures (laparoscopic Nissen fundoplication) for management of chronic GERD. ■

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