Endoscopic management of gastroesophageal reflux disease: A review

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Gastroesophageal reflux disease is the most common esophageal disorder encountered in the United States. Gastroesophageal reflux disease symptoms are associated with a negative quality of life and increased healthcare costs and therefore require an effective management strategy. Although proton pump inhibitors remain the primary treatment of gastroesophageal reflux disease, they do not cure the disorder and can leave patients with persistent symptoms despite treatment. Moreover, patients are still at risk of developing such complications as peptic strictures, Barrett’s metaplasia, and esophageal cancer. Although laparoscopic Nissen fundoplication has been the conventional alternative treatment for those patients who develop complications of gastroesophageal reflux disease, have intractable symptoms, or wish to discontinue taking proton pump inhibitors, investigators have persisted in developing a number of endoscopic approaches to the treatment of gastroesophageal reflux disease. The present report reviews the history of endoscopic treatments devised for the management of gastroesophageal reflux disease and explores the published data and outcomes associated with the latest approach—endoscopic fundoplication using the EsophyX2 device. (J Thorac Cardiovasc Surg 2012; 143:1-6)

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder encountered in the United States.1 Studies have shown that up to 11% of all Americans experience daily reflux symptoms, and one third have symptoms at least once every 3 days.2 GERD is associated with a negative effect on patients’ quality of life, an increase in healthcare costs, and an enormous economic effect on both employers and employees.3 Because of the cumulative effect of this medical disorder, an effective management strategy is essential.

Although proton pump inhibitors (PPIs) constitute the primary treatment of most patients who present with GERD,4-5 they do not cure the disorder, and patients can still have persistent symptoms despite maximal medical treatment. Several reports have suggested that treatment failure occurs in up to 40% of patients with GERD, and 50% to 75% of patients have a relapse of symptoms with cessation of medical treatment.6-8 Moreover, even with treatment, patients can develop peptic strictures, Barrett’s metaplasia, and esophageal adenocarcinoma. Recent data have also suggested an increasing risk with chronic PPI use, including osteoporosis,9 Clostridium difficile infection,10 and adverse interactions with some cardiac medications.11

For those who develop complications, have intractable symptoms, or wish to discontinue medical therapy, surgical intervention with laparoscopic Nissen fundoplication is the conventional alternative approach. It has been associated with great efficacy in treating acidic and nonacidic reflux in patients with either typical symptoms or laryngopharyngeal reflux.12,13 Nevertheless, antireflux operations can lead to a new set of postoperative symptoms, such as dysphagia and bloating,14-16 and might have poorer outcomes when performed in low-volume community settings instead of high-volume centers.17

For many years, the development of a totally endoscopic approach for GERD has been the focus of much intense effort. The present report reviews the history and evolution of the technologies that have been developed to treat GERD endoscopically. Also, endoscopic fundoplication using the latest Food and Drug Administration–approved technology—the EsophyX2 device (EndoGastric Solutions, Redmond, Wash)—is described in detail, and the most recent outcomes data for this approach are reviewed.

HISTORY OF ENDOSCOPIC TREATMENT OF GERD

For more than a decade, endoscopic therapies have been explored to treat GERD in patients who typically do not have a large hiatal hernia, extensive Barrett’s metaplasia, or severe esophageal inflammation and ulceration. In general, these initial strategies aim to decrease the compliance of the gastroesophageal junction and the number of transient relaxations of the lower esophageal sphincter (LES), thereby reducing the frequency and volume of reflux and alleviating the GERD symptoms. These approaches fall into 1 of 4 categories: radiofrequency therapy, mucosal plication, implantation of biopolymers, and full-thickness plication.

Radiofrequency therapy involved the application of radiofrequency energy to the esophageal submucosa to decrease the compliance of the gastroesophageal junction. This strategy used the Stretta system (Curon Medical, Sunnynvale, Calif). This system consisted of a flexible catheter with a balloon–basket assembly that was positioned over a guidewire at the level of the Z line. After positioning, 4
The evolution of endoscopic techniques to treat reflux ultimately led to full-thickness plication. The general approach involved performing a full-thickness plication in the region of the gastric cardia or fundus to decrease LES compliance and restrict relaxation of the LES. The Plicator (NDO Surgical, Mansfield, Mass) was a device that was advanced over a guidewire into the alimentary tract and, under endoscopic guidance, positioned in retroflexion to perform a plication in the cardia of the stomach. The device had a tissue retractor and a polytetrafluoroethylene-pledgeted suture that secured the plication. Initial studies with the Plicator demonstrated very promising outcomes after 3 months of follow-up. Moreover, in 2008, a study of 33 patients who were treated with the Plicator approximately 1 cm below the gastroesophageal junction and followed up for 5 years was reported. Of the 33 patients, 67% continued to not require daily PPI therapy, and a significant improvement in GERD health-related quality of life (HRQL) scores persisted (median preoperative score vs median score at follow-up, 19 vs 10; P < .001). However, the availability of the Plicator device ceased after NDO Surgical went out of business in 2008.

ENDOSCOPIC PARTIAL FUNDOPICATION

With the evolution of endoscopic therapies advancing in the realm of full-thickness plication, the EsophyX2 device (EndoGastric Solutions) was developed to achieve a partial fundoplication through an endoscopic approach. The EsophyX2 device has a tubular shape and fits over an endoscope. On the end that is advanced through the mouth and into the alimentary tract, it has a screw-shaped helical retractor that is advanced and anchored to the Z line. Retraction on the Z line using the helical retractor helps to reconstitute the angle of His, which contributes to the anti-reflux mechanism.

The gastric fundus is approximated to the distal intrabdominal esophagus by closure of the tissue mold. In cases in which a small hiatal hernia is present, suction can be applied along the shaft of the device, bringing the esophagus into close apposition with the device. Because traction is also maintained distally with the helical retractor at the
gastroesophageal junction, when the whole device is advanced into the mouth and esophagus, small hiatal hernias can be reduced before fundoplication. Two stylets are used to deploy 2 polypropylene sutures, fashioned as H-shaped fasteners, that anchor the fundus to the esophagus. The sutures are placed along 2 semicircumferential rows opposite the lesser curvature, 1 proximal to the other, until an omega-shaped wrap of 270° and 2 cm length is created. This procedure typically requires approximately 12 to 20 sutures and excludes the lesser curvature to avoid injury to the vagus nerves. Although a small hiatal hernia can be reduced during creation of the wrap, herniorrhaphy is not achievable with this technique.

Two physicians are usually involved with each procedure. One acts as the endoscopist and the other operates the device during each procedure. To optimize visibility, the stomach can be insufflated with carbon dioxide gas from a laparoscopic insufflation system that is set to a pressure of 12 mm Hg to 15 mm Hg, and complete muscle relaxation is achieved with the administration of a paralytic medication. After completing the wrap and removing the device, repeat endoscopy is performed to evacuate air and accumulated secretions and to inspect the valve. Typically, patients are observed overnight, undergo a barium esophagogram the next morning to evaluate for a leak (because of the extent of manipulation about the gastroesophageal junction), and are discharged after tolerating a clear-liquid diet.

RESULTS OF ENDOSCOPIC FUNDOPLICATION WITH ESOPHYX2

To date, approximately 22 peer-reviewed reports have been published regarding endoscopic fundoplication with the Esophyx system. Many of the pertinent studies have been reviewed in the present report and listed in Table 1.27-34

The initial experience with endoscopic fundoplication was reported from Europe. Cadière and colleagues27 were the first group of investigators to publish their experience with endoluminal fundoplication in Belgium in 2008. In their series, 17 patients who had chronic, typical GERD for a median of 10 years (range, 3–15 years), PPI dependence (median use, 6 years; range, 2–13 years), and no esophageal dysmotility underwent endoluminal fundoplication. Thirteen patients had small hiatal hernias. Postoperatively, no serious complications developed. At 1 year of follow-up, the median GERD-HRQL scores had improved significantly (preoperative score of 17 vs postoperative score of 6; P = .02), with complete discontinuation of PPIs in 82% of the patients. Additionally, 16 of the 17 patients underwent subsequent endoscopic evaluation, which revealed that the wraps had become loose in 3 patients, and were moderately to tightly adherent to the endoscope in 13 patients. Also, the median circumference of the valves was 200°; the median length was 3 cm, and hiatal hernias remained reduced in 62% of the patients. These investigators subsequently reported the 2-year results28 of the same series of patients. The 2-year assessment included responses to the GERD-HRQL questionnaire, endoscopy, medication use, and questions related to diet and lifestyle activity changes. Also, the valve length (from the apex of the fundus to the valve lip), circumference (as the distance in degrees between the 2 most distant points of the esophagogastric valve), and Hill grade were determined. Of the 17 patients who had undergone endoscopic fundoplication, 14 (82%) completed the 2-year follow-up studies; of the remaining 3, 2 had undergone retreatment and 1 was lost to follow-up. No patient had any adverse complications. The improvement in GERD-HRQL scores remained statistically significant (17 vs 7; P = .004), and 86% of the patients were satisfied with the outcomes of the procedure. Ten patients had successfully discontinued PPIs. Also, 79% of patients had either complete cure or remission of GERD 2 years after endoscopic fundoplication.

<table>
<thead>
<tr>
<th>Investigators (y/patients [n])</th>
<th>Follow-up (m)</th>
<th>PPIs stopped (%)</th>
<th>GERD-HRQL score (preoperative; postoperative)</th>
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<tbody>
<tr>
<td>Cadière et al27 (2008, n = 17)</td>
<td>12</td>
<td>82</td>
<td>17; 6</td>
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<tr>
<td>Cadière et al28 (2009, n = 14)</td>
<td>24</td>
<td>59</td>
<td>17; 7</td>
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<tr>
<td>Cadière et al27 (2008, n = 84)</td>
<td>12</td>
<td>85</td>
<td>24; 7</td>
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<td>Hoppo et al30 (2010, n = 19)</td>
<td>10.8</td>
<td>26</td>
<td>NA</td>
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<td>Testoni et al* (2010, n = 20)</td>
<td>6</td>
<td>55</td>
<td>45; 16</td>
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<td>Dennytenaere et al31 (2010, n = 26)</td>
<td>10</td>
<td>35 (plus 21% decreased)</td>
<td>22; 10</td>
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<tr>
<td>Velanovic32 (2010, n = 24)</td>
<td>7 wk</td>
<td>79</td>
<td>25; 5</td>
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<td>Repici et al (2010, n = 20)</td>
<td>12</td>
<td>47</td>
<td>40; 10</td>
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<tr>
<td>Barnes et al33 (2011, n = 123)</td>
<td>7</td>
<td>83</td>
<td>28; 2</td>
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<td>Narasule et al34 (2012, n = 46)</td>
<td>4.7</td>
<td>52.2</td>
<td>23; 7</td>
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Additionally, in 2008, a European multicenter experience was reported involving 7 centers with 12-month results.29 A total of 84 patients with chronic GERD underwent transoral incisionless fundoplication (TIF). Three perioperative complications developed. Two esophageal perforations occurred on insertion of the device into the alimentary tract, and one patient developed postoperative bleeding requiring a 4-unit blood transfusion. Of the 84 patients, 79 completed follow-up assessment tests at 12 months. The GERD-HRQL scores improved significantly (median pre-TIF score, 24 vs post-TIF score, 7; \( P < .0001 \)), with improvements in the score of \( \geq 50\% \) among 73\% (n = 58) of the treated patients. Also, 85\% of the patients had discontinued daily PPI use at 1 year, with 68\% having stopped taking PPIs completely. Furthermore, according to the symptom reduction and PPI discontinuation, GERD was considered cured in 56\% of the patients. In addition, according to preoperative and postoperative esophageal pH monitoring, there was a significant reduction in the median esophageal acid exposure time (10 minutes vs 7 minutes; \( P = .02 \)) and a reduction of the median DeMeester score (median, 34 vs 28; \( P < .001 \)) at 12 months of follow-up.

In the United States, to establish the anatomic and physiologic basis of the endoscopic fundoplication using the EsophyX device, Jobe and colleagues reported their experience in a 2-phase study using a canine model in 2008. That report evaluated 2 separate techniques of placement of the H-shaped polypropylene sutures: the TIF 1.0 technique (in which suture placement begins in the center of wrap and extends bilaterally around the gastroesophageal junction in a single layer) and the TIF 2.0 technique (in which suture placement starts at each end and extend toward the center of each row around the intra-abdominal esophagus in 2 layers). In the first phase, 21 dogs were treated with the TIF 1.0 procedure and killed at 4 weeks, 12 weeks, or 1 year after the procedure. Pathologic examination demonstrated fusion of the serosa at the points of fundoplication, which had been durable. The mean Hill grades for the valves—at baseline and after the procedure—were statistically significant and persisted even at necropsy. In the second phase, 7 dogs each underwent the TIF 1.0 procedure, the TIF 2.0 procedure, and a sham procedure. The dogs that underwent TIF 2.0 had increased LES pressure and length 2 weeks after the procedure that was significantly different from the baseline measurements and was superior to that achieved with the TIF 1.0 technique. That report supported the anatomic basis of the TIF 2.0 procedure and also suggested that the procedure might be durable because of the formation of adhesions.

Despite this promising work, a multicenter study involving 1 American and 2 Australian institutions was reported in 2010 in which 19 patients with typical GERD symptoms, positive pH testing, failed management with PPIs, and no or small hiatal hernias (\( \leq 2 \) cm) underwent endoscopic fundoplication using the TIF 2.0 technique. Despite the small number of enrolled patients, 3 major complications occurred: 1 patient had an esophageal perforation, 1 had alimentary tract bleeding requiring transfusion, and 1 developed permanent numbness of the tongue. After a mean follow-up of 10.8 months, the symptomatic failure rate was unusually high. Of the 19 patients, 10 had subsequently undergone laparoscopic Nissen fundoplication for recurrent GERD symptoms and endoscopically confirmed wrap disruptions. Furthermore, only 5 of the 19 patients had successfully stopped taking PPIs and only 3 patients had decreased the PPI dose. Interestingly, 4 patients each were enrolled from the 2 Australian centers, and the remaining 11 patients were enrolled from the University of Pittsburgh. Because the patients enrolled from each of the centers likely represented the initial experience of endoscopic fundoplication at each institution, it is perhaps not such a surprise that the rate of symptomatic failure was accordingly high.

Other American investigators have reported their experience with endoscopic fundoplication with promising results. Demyttenaere and colleagues described their experience with 26 patients, of whom 22 patients had a mean follow-up period of 10 months. There were 3 symptomatic failures (11.5\%) that were managed by subsequent fundoplication. A statistically significant decrease in the GERD-HRQL score was seen at the 3-month postoperative visit (22 vs 10; \( P = .0007 \)), but only 45\% of the patients had a \( \geq 50\% \) decrease in the GERD-HRQL score. Also, although PPI use had decreased, 68\% of the patients were using PPIs compared with 100\% preoperatively. Furthermore, at a mean of 10 months of follow-up, 45\% of the patients were satisfied and 30\% were dissatisfied.

In 2010, Velanovich reported his experience with 26 patients, 24 of whom successfully underwent endoscopic fundoplication. Two patients were not treated because of an inability to pass the device. Of the 24 patients, 20 had typical symptoms and 4 had symptoms of laryngopharyngeal reflux. Four of the patients had previously undergone Nissen fundoplication and had recurrent symptoms. There was 1 perioperative complication involving a patient with a gastric mucosal tear that led to bleeding that required a blood transfusion. With a mean duration of follow-up of 7 weeks, 19 of 24 patients were satisfied with the alleviation of symptoms. The median GERD-HRQL score improved from 25 to 5 (\( P = .0004 \)). In a subsequent letter to the Editor, Velanovich updated this series with 2 additional patients who had recurrent GERD owing to failure of the endoluminal fundoplication, both of whom required subsequent laparoscopic Nissen fundoplication.

In 2011, Barnes and colleagues reported the first American multicenter experience of endoscopic fundoplication. In their series, 124 patients underwent attempted endoscopic fundoplication at 2 community hospitals. Of these,
123 were successfully completed; 1 was aborted owing to a hematoma in a patient who had been taking aspirin and warfarin therapy. Five patients had experienced an early return of symptoms and were treated with Nissen fundoplication. Follow-up evaluations were conducted for 110 patients (89%) at a median interval of 7 months. The median GERD-HRQL scores were significantly reduced from 28 to 2 \((P < .001)\). The median reflux symptom index scores were also significantly reduced from 29 to 4 \((P < .001)\). In terms of typical symptoms, significantly fewer patients complained of heartburn (92% vs 19%; \(P < .001\), regurgitation (85% vs 12%; \(P < .001\)), and dysphagia (68% vs 15%; \(P < .001\)) after endoscopic fundoplication. For atypical symptoms, significant reductions were found in the incidence of hoarseness (53% to 5%, \(P < .001\), clearing of the throat (82% to 15%, \(P < .001\), excess throat mucus or postnasal drip (75% to 15%, \(P < .001\)), cough (70% to 15%, \(P < .001\)), and globus sensation (77% to 12%, \(P < .001\)). Moreover, 8 patients were using PPIs either occasionally \((n = 4)\) or daily \((n = 4)\), and the remaining 102 patients were no longer taking PPIs.

Also, in 2011, Bell and Freeman\(^{37}\) reported on their experience in treating 37 patients with endoscopic fundoplication. Of the 37 patients, 32 had typical symptoms (ie, heartburn or regurgitation) and 68% had GERD-associated cough, asthma, or aspiration as a chief complaint. With a median follow-up of 6 months, a significant improvement was seen in 64% of patients with atypical symptoms and in 70% to 80% of patients with typical symptoms, according to the GERD-HRQL and reflux symptom index score reduction of 50% or more compared with the baseline data. In addition, the reflux characteristics were significantly improved or normalized in 61% and 56% of the patients in terms of esophageal acid exposure and DeMeester scores, respectively. Of the 37 treated patients, 5 (13.5%) required subsequent interventions (2 patients with repeat endoscopic fundoplication and 3 patients with laparoscopic Nissen fundoplication).

More recently, we reported our initial experience with endoscopic fundoplication at Boston Medical Center.\(^{34}\) A total of 46 patients were treated with endoscopic fundoplication, after a preoperative workup that included manometry, barium esophagogram, endoscopy, and a pH study if patients had atypical symptoms or a lack of response to PPIs with typical symptoms. Although the mean operative time was 83 minutes for the entire series, a learning curve was demonstrated because the mean operative time for the first 5 cases was significantly longer than that for the subsequent cases (122 vs 78 minutes; \(P = .001\)). One major complication involved the readmission of a patient with aspiration pneumonia. Minor complications occurred in 3 patients, including 1 patient with gastric bleeding at a suture site (but not requiring transfusion) and 2 patients with urinary retention. With a mean follow-up of 140 days, the mean GERD-HRQL scores improved significantly (23 vs 7; \(P < .001\)) and remained significant even when only those patients with follow-up longer than 90 days (mean follow-up, 240 days) were considered separately \((n = 22, 23 \text{ vs } 8; P = .001)\). Four of these patients had no symptomatic improvement, 3 because of wrap disruption, and were treated with repeat endoscopic fundoplication (2 patients) or laparoscopic Nissen fundoplication (1 patient).

Finally, a group from the Czech Republic recently reported a single-center, randomized trial comparing transoral incisionless fundoplication and laparoscopic Nissen fundoplication for the treatment of GERD.\(^{38}\) Thirty-four patients were enrolled in the endoscopic fundoplication group—of which the Plicator was used for 18 patients and the EsophyX for 16 patients—and 18 patients underwent laparoscopic Nissen fundoplication. At 12 months after the procedure, 26 patients in the endoscopic fundoplication group and 14 patients in the laparoscopic Nissen fundoplication group had been seen in follow-up. Significant improvements were seen in the GERD-HRQL scores for both the endoscopic fundoplication group (preoperative mean score of 21.2 vs postoperative mean score of 6.6; \(P < .0001\)) and the laparoscopic fundoplication group (preoperative mean score of 19.3 vs 6.7; \(P < .0001\)). The mean hospital stay was significantly shorter in the group of patients who underwent endoscopic fundoplication than for those patients who underwent laparoscopic Nissen fundoplication (2.9 vs 6.4 days; \(P < .0001\)).

**CONCLUSIONS**

After a decade of evolution, endoscopic fundoplication is becoming a reasonable alternative treatment for the patient with chronic GERD with small hiatal hernias. Multiple series have suggested that this approach is safe and effective in short-term follow-up. Nevertheless, more information is needed to determine the durability of the fundoplication in patients with long-term follow-up, the efficacy for atypical symptoms of reflux, and the comparability with respect to laparoscopic Nissen fundoplication.

**References**


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Endoscopic approaches for the treatment of GERD have been the focus of intense efforts during the past decade. The present report describes the history of endoscopic therapies for GERD and reviews the current data for endoscopic fundoplication.