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The LINX® reflux management system: confirmed safety and efficacy now at 4 years

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Abstract
Background Sphincter augmentation with the LINX® Reflux Management System is a surgical option for patients with chronic gastroesophageal disease (GERD) and an inadequate response to proton pump inhibitors (PPIs). Clinical experience with sphincter augmentation is now available out to 4 years.
Methods In a multicenter, prospective, single-arm study, 44 patients underwent a laparoscopic surgical procedure for placement of the LINX System around the gastroesophageal junction (GEJ). Each patient's baseline GERD status served as the control for evaluations post implant. Long-term efficacy measures included esophageal acid exposure, GERD quality-of-life measures, and use of PPIs. Adverse events and long-term complications were closely monitored.
Results For esophageal acid exposure, the mean total % time pH < 4 was reduced from 11.9 % at baseline to 3.8 % at 3 years ($p < 0.001$), with 80 % (18/20) of patients achieving pH normalization ($\leq$5.3 %). At $\geq$4 years, 100 % (23/23) of the patients had improved quality-of-life measures for GERD, and 80 % (20/25) had complete cessation of the use of PPIs. There have been no reports of death or long-term device-related complications such as migration or erosion.
Conclusions Sphincter augmentation with the LINX Reflux Management System provided long-term clinical benefits with no safety issues, as demonstrated by reduced esophageal acid exposure, improved GERD-related quality of life, and cessation of dependence on PPIs, with minimal side effects and no safety issues. Patients with inadequate symptom control with acid suppression therapy may benefit from treatment with sphincter augmentation.

Keywords Gastroesophageal reflux disease · Sphincter augmentation · Lower esophageal sphincter · Proton pump inhibitors · Nissen fundoplication

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Gastroesophageal reflux disease (GERD) is a common and chronic gastrointestinal disorder [1, 2]. Patients with GERD are routinely prescribed proton pump inhibitors (PPIs). PPIs suppress normal acid production in the stomach to change the acidity of the reflux from acidic to nonacidic or weakly acidic. This approach has proven to be effective for healing esophagitis and managing symptoms such as heartburn, but it less effective for regurgitation and the nonacidic symptoms of GERD [3, 4]. PPIs, however, do not address the reason that reflux occurs, i.e., a dysfunctional lower esophageal sphincter (LES). In GERD, the LES is prone to abnormal opening due to gastric distension, transient relaxation, or hypotensive resting tone [5–7]. Understanding the relationship between the LES and GERD is critical to the development of a physiological therapy that will prevent reflux without limiting the dynamic nature of the LES to open for gastric venting or swallowing. The intent of sphincter augmentation with the LINX Reflux Management System (Torax Medical, St. Paul, MN) is to improve the barrier function of the LES without restricting the opening of the LES to normal physiological functions. It is a novel device with a mechanism of action unlike other devices currently or previously used to treat GERD. Clinical experience with sphincter augmentation is now available out to 4 years.

Materials and methods

Patients

Between February 2007 and October 2008, 44 patients were implanted with the LINX System at four study centers in the US and Europe. All patients were between 18 and 75 years of age, candidates for antireflux surgery, had documented typical symptoms of GERD for at least 6 months, and were taking daily PPIs and had an incomplete symptom response to PPIs. Abnormal esophageal acid exposure while off PPI therapy was confirmed in all patients. Exclusion criteria were hiatal hernia $\geq$3 cm as determined by endoscopy, erosive esophagitis grade B, C, or D (Los Angeles classification), body mass index >35, Barrett's esophagus, motility disorders, gross esophageal anatomic abnormalities, and a known allergy to titanium, stainless steel, nickel, or ferrous materials. Baseline assessments included medical history, medication use, the GERD Health-Related Quality of Life (GERD–HRQL) questionnaire, pH testing, esophageal manometry, endoscopy, and barium esophagram [8].

Study design and oversight

The study was a prospective, multicenter, single-arm, controlled clinical trial where patients served as their own control, comparing each individual patient's baseline data to data collected post implant to assess the effect of treatment on esophageal acid exposure, symptoms, and GERD medication use. The short-term and midterm results of this trial have already been reported [9, 10]. The FDA provided an investigational device exemption (IDE G060172) to conduct this study, trial protocol was approved by the institutional review board at each study center, and written informed consent was obtained from all participants.

Device and procedure

Sphincter augmentation improves the reflux barrier via the use of a flexible and expandable device that creates resistance to abnormal opening of the sphincter rather than adding bulk to the LES or tightening the sphincter by plication or radiofrequency ablation [11, 12]. The device consists of a series of interlinked titanium beads containing a magnetic core (Fig. 1). Each bead is connected by

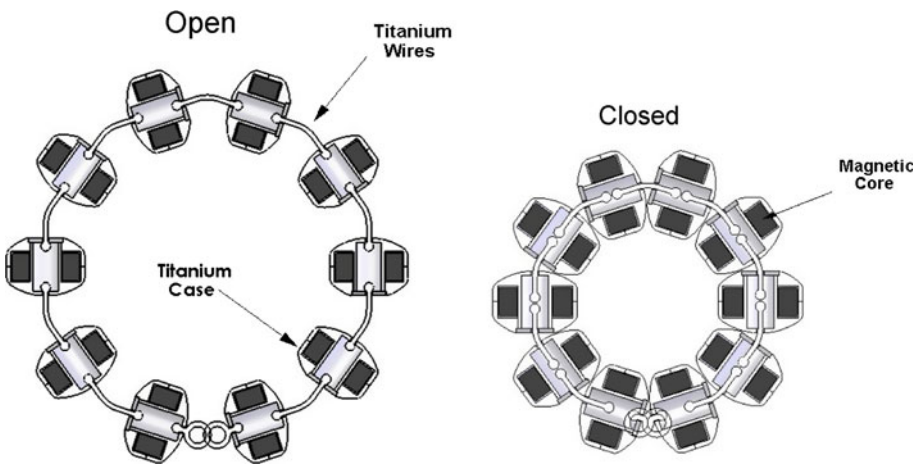

Fig. 1 Cross section of the LINX device in open and closed positions

titanium wires of a specific length that limit the distance any two cores can spread apart. Each bead can move independent of the other beads. The implant can be manufactured to different lengths, based on the number of beads linked together, to accommodate the varied external esophageal diameters. The device is placed laparoscopically around the external esophagus at the gastroesophageal junction (GEJ) to aid the native sphincter in its ability to resist opening and prevent reflux into the esophagus (Fig. 2A). When a patient swallows a food bolus, the peristaltic pressure overcomes the magnetic attraction and the device opens (Fig. 2B). As the peristaltic pressure drops, the device is drawn closed by the attraction between the magnetic cores of adjacent beads. At rest, the device encircles the GEJ like a "Roman arch," with each magnet resting against its neighbor, to avoid compression of the tubular esophagus (Fig. 2C). The surgical technique to place the device has been previously described [9, 10]. Briefly, the device is placed laparoscopically with the patient under general anesthesia. The target location of the magnetic implant is the lower esophageal sphincter identified as found in the area between the origin of the inferior leaf of the phrenoesophageal ligament and the hepatic branch of the anterior vagus nerve. The anterior wall of the abdominal esophagus is exposed between these two landmarks. The retroesophageal dissection begins along the anterior border of the right crus just cephalad to the decussation of the crura. The posterior vagal trunk is identified. The same dissection is repeated along the left crus of the diaphragm. Gentle dissection from the right opens the retroesophageal window, and a tunnel is created between the posterior esophageal wall and the posterior vagal trunk. A Penrose drain is passed through the tunnel to encircle the esophagus. A sizing tool is advanced through the tunnel and wrapped around the tubular esophagus above the hepatic branch of the anterior vagal trunk. The appropriate sized device to be implanted is selected and inserted and the ends secured. Care is taken to ensure that the device does not compress the tubular esophagus and is not sutured to the esophageal wall.

Long-term assessment of efficacy and safety

A patient's baseline evaluations served as the comparison point for post-implant evaluations. Esophageal pH testing was performed out to 3 years at one European study center. The other sites performed pH testing out to 1 year. Measurements collected as part of pH testing included total % time with pH < 4, upright % time with pH < 4, supine % time with pH < 4, number of episodes, number of episodes longer than 5 min, longest episode, and DeMeester score (composite of all parameters) [13]. Esophageal pH post implant was considered normalized if the total % time pH < 4 was ≤ 5.3 %. GERD-related symptoms were evaluated with the GERD-HRQL questionnaire. This validated questionnaire consists of six heartburn-related questions, two swallowing-related questions, one gas bloating question, and one question related to medication use. Patients provide a response to each question on a scoring scale of 0–5 (Table 1). The total score for the GERD–HRQL ranges from 0 to 50, with higher scores indicating worse symptoms. GERD medication use and

Table 1 GERD–HRQL scoring scale

0	No symptoms
1	Symptoms noticeable but not bothersome
2	Symptoms noticeable and bothersome but not every day
3	Symptoms bothersome every day
4	Symptoms affect daily activities
5	Symptoms are incapacitating; unable to do activities

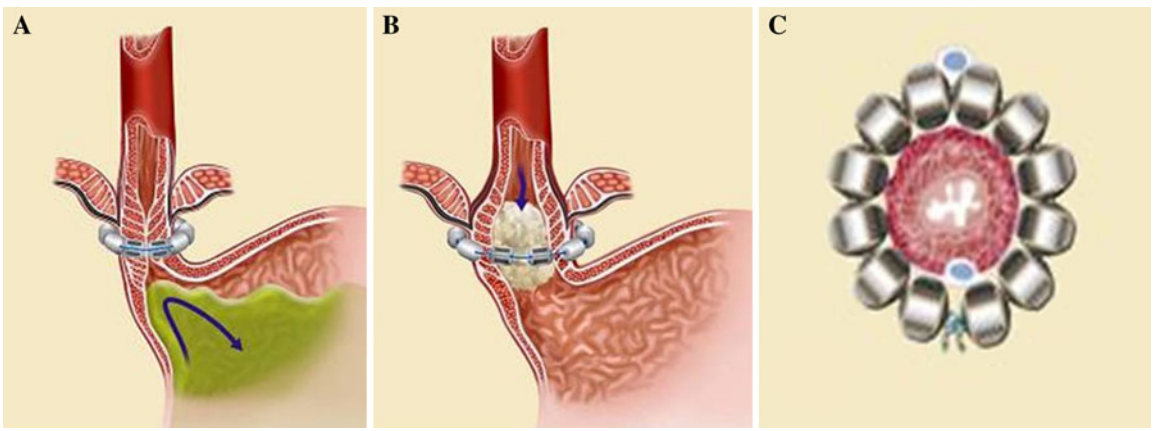

Fig. 2 **A** The LINX device in the closed position. **B** The LINX device in the open position. **C** The closed position showing no compression of the esophageal wall

adverse events were queried about at every visit. An adverse event related to the device was considered serious if it resulted in death; was life-threatening; required hospitalization longer than 24 h; required prolongation of a current hospitalization; resulted in persistent or significant disability/incapacity; resulted in fetal distress, fetal death, or a congenital anomaly or birth defect; and required intervention to prevent permanent impairment or damage.

Statistical analysis

All other analyses were conducted on available data. The two-tailed, paired Student *t*-test was used to compare pre- and postoperative values; differences were considered significant at the $p < 0.05$ level.

Results

Baseline and procedural results

We studied 44 patients (26 males and 18 females, mean age = 42.8 years) with long-standing histories of GERD and chronic use of PPIs. The implant procedure was performed via a laparoscopic approach using surgical techniques familiar to surgeons who perform fundoplication. The median operative time was 40 min (range = 19–104), defined as the time from all ports placed to when the first port was removed. All implants were completed without crossover to fundoplication. No intraoperative complications were reported. All patients except one were discharged within 48 h. No patients required extended hospitalization due to an adverse event. Patients were instructed to resume a normal diet as soon as tolerated following implant to promote actuation of the device during healing (i.e., separation of beads by a food bolus during swallowing).

Long-term efficacy results

Patients have been followed at regular intervals since implant. Median follow-up time was 3.7 years or 1,343 days (range = 119–1,827 days). Esophageal pH testing was completed in 20 patients at 3 years. The mean total acid exposure time was reduced from 11.9 ± 8.0 to 3.8 ± 3.4 % ($p < 0.001$ (Table 2). Normalization of pH was achieved in 77, 90, and 80 % of patients at 1, 2, and 3 years, respectively. The mean total GERD–HRQL score of patients off PPIs at 4 years or more was 3.3 ± 3.7 compared to the baseline score of 25.7 ± 6.4 ($p < 0.001$). All patients (23/23) had at least a 50 % reduction in the total GERD–HRQL score at 4 years. Satisfaction remained high at 4 years while off PPIs, with 87.5 % of patients reporting satisfaction with their present condition compared to 0 % at baseline. Patients showed improvement in gas bloat symptoms following treatment as assessed by the GERD–HRQL questionnaire. The median score at baseline was three (symptoms bothersome every day) and improved at 4 years to zero (no symptoms). At baseline, all patients required daily PPIs to manage GERD-related symptoms. Following sphincter augmentation, 80 % of patients were free from daily dependence on PPIs (Table 3).

Table 2 Esophageal pH results by visit: parameters of esophageal acid exposure and the composite DeMeester Score at 1–3 years after surgery

	Baseline ($n = 44$)	1 year ($n = 39$)	2 years ($n = 20$)	3 years ($n = 20$)
Total % time pH < 4	11.9	3.1	2.3	3.8
Upright % time pH < 4	13.6	3.2	2.9	4.4
Supine % time pH < 4	8.3	2.8	1.1	2.6
No. episodes	112.5	48.9	51.8*	70.2*
No. episodes >5 min	7.0	3.3	2.4	4.5*
Longest episode (min)	37.4	12.5	12.9	16.0
DeMeester score	42.3	12.5	9.1	14.7
% Of patients with pH normalization[a]	NA	77 %	90 %	80 %

Values are means

[a] Normalization defined as total % time pH < 4 for <5.3 %

* Indicates $p > 0.05$ for the comparison between baseline and follow-up. Absence of symbol indicates statistical significance ($p < 0.05$)

Safety results and side effects

At 4 years, 95.5 % (42/44) of patients were free from a serious adverse event (SAE) related to the device or implant procedure. The device/procedure-related SAEs included one patient who had persistent dysphagia that resolved following removal of the device 226 days after implant. This patient underwent a Nissen fundoplication at a later date. Another patient experienced chest pain 22 days post implant and was hospitalized. Intervention included the use of sublingual nitroglycerin for suspected esophageal spasm. The patient was discharged after a short hospital stay and the pain resolved <2 months post implant. No device/procedure-related SAEs occurred beyond 1 year. There have been no reports of device erosion or migration.

The most common adverse event reported was dysphagia in 43 % (20/44) of patients. The dysphagia was generally mild and resolved by 3 months. All patients were able to return to a normal diet postoperatively. There were no reports of food impaction or inability to eat when patients resumed a normal diet, typically on postoperative day 1 following radiological assessment of esophageal transit.

Table 3 Mean baseline and postoperative scores from GERD–HRQL questionnaire measured off PPIs

	Baseline ($n = 44$)	1 year ($n = 39$)	2 years ($n = 35$)	3 years ($n = 31$)	4 years ($n = 23$)
How bad is your heartburn?	3.7 (4.0)	0.6 (0.0)	0.6 (0.0)	0.6 (0.0)	0.5 (0.0)
Heartburn when lying down?	3.1 (3.0)	0.4 (0.0)	0.3 (0.0)	0.4 (0.0)	0.2 (0.0)
Heartburn when standing up?	3.3 (3.0)	0.4 (0.0)	0.4 (0.0)	0.3 (0.0)	0.3 (0.0)
Heartburn after meals?	3.6 (4.0)	0.6 (0.0)	0.5 (0.0)	0.6 (0.0)	0.7 (0.0)
Does heartburn change your diet?	3.1 (4.0)	0.2 (0.0)	0.6 (0.0)	0.6 (0.0)	0.5 (0.0)
Does heartburn wake you from sleep?	2.5 (3.0)	0.3 (0.0)	0.3 (0.0)	0.3 (0.0)	0.0 (0.0)
Do you have difficulty swallowing?	1.2 (1.0)	0.6 (0.0)	0.2 (0.0)	0.3 (0.0)	0.4 (0.0)
Do you have bloating and gassy feelings?	2.9 (3.0)	0.5 (0.0)	0.5 (0.0)	0.4 (0.0)	0.4 (0.0)
Do you have pain with swallowing?	0.6 (0.0)	0.1 (0.0)	0.0 (0.0)	0.1 (0.0)	0.0 (0.0)
If you take medication, does this affect your daily life?	2.0 (2.0)	0.2 (0.0)	0.4 (0.0)	0.5 (0.0)	0.2 (0.0)
Total GERD score (mean ± SD)	25.7 ± 6.4	3.8 ± 4.0	3.83. ± 7.0	3.93 ± 5.5	3.33 ± 3.7
How satisfied are you with your present condition?[a]	0 %	87 %	80 %	88 %	87 %
% Of patients achieving at least a 50 % reduction in total GERD-HRQL score compared to baseline	NA	9 7%	89 %	91 %	100 %

Values are mean (median)

[a] % Satisfied

In addition to the patient who had the device removed because of dysphagia, two other patients had the device electively removed for reasons other than a device-related adverse event. One patient had the device removed 468 days after implant in order to have an MRI evaluation of his neurological symptoms. Another patient had continued symptoms of GERD and elected to have a Nissen fundoplication 1,302 days post implant. No deaths, permanent injuries or disabilities, or complications associated with device removal have been reported. Improvement in the reflux barrier was achieved without significant side effects. Complaints of inability to belch or vomit were reported in <5 % of patients (2/44).

Discussion

Sphincter augmentation improved the barrier function of the LES as evidenced by significant reductions in distal esophageal acid exposure, improved symptom control, and discontinuation of the use of PPIs in patients now followed for 4–5 years. Notably, long-term complications and safety issues such as device erosions or migrations have not emerged. In theory, the device was designed to minimize the risk of device erosion, and now this concept has been proven in the clinical setting. Unlike other devices that have been placed around the external esophagus and in the area of the GEJ, sphincter augmentation does not use bulk or rigid materials to prevent reflux. Each bead can move and flex independent of the adjacent beads, creating a flexible and expandable implant intended to mimic the physiological movement of the esophagus. This is critically important in that the device responds to the esophagus rather than limiting its range of motion, and it avoids compression and tension that can lead to erosion. When implanting the device, a tunnel is created between the posterior esophageal wall and the posterior vagal trunk where the device is passed through and then wrapped around the esophagus and the ends are then secured to each other. This approach may help anchor the device in place during the early stages of healing. Once healing is complete, as seen in animal studies and from observations during device removal in this clinical study, the device is fully encapsulated in fibrous tissue and the device is confined to the adventitia adjacent to the muscular wall of the esophagus, making migration proximal or distal from the implant unlikely.

Also important is that sphincter augmentation does not replace or reconstruct the existing LES. As described above, the device is not incorporated into the esophageal wall; this makes it possible to remove the device without altering the esophageal anatomy or compromising future treatment options. During the study, a total of three patients had the device laparoscopically removed (between days 226 and 1,302 post implant). Surgical removal can be accomplished without difficulty or significant dissection. The removal involves releasing each individual bead from a pocket of connective tissue. There was no increase in the technical difficulty of removing a device that had been implanted for a longer duration. Nissen fundoplication was performed in two of the patients following removal of the device. The ability to safely remove the device should be

considered a strength of sphincter augmentation as it provides the surgeon with a minimally invasive and preservative approach in the event device removal is elected. In comparison, revision of a Nissen fundoplication or transoral incisionless fundoplication has been shown to carry increased risk for complications and to be technically more challenging [14–16].

The excellent safety profile at long-term follow-up is matched by sustained clinical benefit to the patient. Objective evidence in the form of pH normalization was seen in 80 % of patients at 3 years. These results are unprecedented for a medical device used to treat GERD. Clinical outcomes associated with sphincter augmentation included improved GERD-related quality-of-life scores and discontinuation of PPIs long term. These clinical benefits were not diminished by side effects such as the inability to belch or vomit and increased gas bloat. Patients, who would otherwise be candidates for surgical GERD treatment, often forgo antireflux surgery because of concerns about gas bloat side effects associated with Nissen fundoplication. For these patients, sphincter augmentation may be a better alternative.

A limitation of our study was that patients with GERD complicated by large hernias, Barrett's esophagus, advanced esophagitis, or motility disorders were not included. For these patients, Nissen fundoplication may be the best option. Because fundoplication reconstructs the LES by wrapping the fundus around the lower esophagus, it relies less on the native LES to contribute to the reflux barrier and may be better suited to a severely diseased LES. Additional research is needed to determine if sphincter augmentation should be considered for patients with the conditions excluded from this study.

In conclusion, we found sphincter augmentation with the LINX Reflux Management System to be a safe and effective treatment for patients with chronic GERD and incomplete symptom relief while taking PPIs. Device erosion and migration have not been reported and clinical benefits have been maintained long term. Sphincter augmentation is an alternative surgical treatment option to improve the reflux barrier and has the potential to improve the lives of patients suffering from GERD without causing harm and significant side effects.

Disclosures Drs. Tom DeMeester, Luigi Bonavina, Robert Ganz, and Paul Fockens have been or currently are consultants for Torax Medical. Drs. John Lipham, Greta Saino, Daniel Dunn, and Willem Bemelman have no conflicts of interest or financial ties to disclose.

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