



Long-term (15-year) objective evaluation of 150 patients after laparoscopic Nissen fundoplication

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ABSTRACT

Introduction: Laparoscopic Nissen fundoplication is the preferred operative treatment for patients with gastroesophageal reflux disease. The most recent published results only refer to clinical evaluations and few discuss objective measurements. Our purpose was to determine the late results of laparoscopic Nissen fundoplication, performing clinical, endoscopic, histologic, and functional studies.

Material and methods: A total of 179 patients were included in a prospective study. All had gastroesophageal reflux disease symptoms of at least 5-year duration, daily dependence on proton pump inhibitors, and a type I hiatal hernia less than 5 cm. Exclusion criteria included Barrett's esophagus, hiatal hernia >5 cm, failed antireflux surgery, and obesity (body mass index >30). We performed a radiologic study, 3 or more endoscopic procedures with biopsy samples of the antrum and esophagogastric junction, esophageal manometry, and 24-hour pH monitoring.

Results: We found that 4 patients (2.2%) died 3–4 years after operation from nonoperative reasons. A total of 25 patients (14%) were lost to follow-up, and 150 patients (83.8%) submitted to late objective evaluations (15 years). Visick I-II symptoms were observed in 79.3% and III-IV (failures) in 20.7%. Endoscopy showed a normal positioning of the esophagogastric junction in the Visick I-II patients and a type III cardia or hiatal hernia with erosive esophagitis in Visick III-IV patients. Short-segment Barrett's esophagus developed in 5.3% of patients. Lower esophageal sphincter pressure remained increased over the preoperative value in all groups. The 24-hour pH monitoring also was decreased over the preoperative value in Visick I-II patients but showed no significant change in Visick III-IV patients. Carditis at the esophagogastric junction regressed to fundic mucosa in 50% of Visick I-II patients.

Conclusion: Laparoscopic Nissen fundoplication produces control of symptoms in 80% of patients late (up to 15 years) after surgeries corroborated by endoscopic, histologic examinations, and functional studies. It is essential to perform these objective evaluations to demonstrate the "antireflux effect" after laparoscopic Nissen fundoplication.

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Introduction

Nissen fundoplication remains the operative technique of choice to treat gastroesophageal reflux disease (GERD) patients through a laparoscopic approach.^{1–11} We found late results (>10 years of follow-up) in 19 publications by 13 surgical teams.^{10,12–29} One group had 4 publications,^{12,15,17,29} another group had 3

reports,^{13,22,27} and another group had 2 publications.^{19,23} The majority of these reports refer only to clinical evaluations, and a few of these reports mention objective analyses of the "antireflux effect" of laparoscopic Nissen fundoplication (LNF).

The goals of this present, prospective study were: (1) to determine the late (15 years) clinical results of LNF, (2) to measure objective evaluations the antireflux effect of the LNF, (3) to achieve at least 80% of follow-up in patients included in the original study, and (4) to determine, by sequential histologic analysis, the development of esophagitis and Barrett's esophagus (BE) after surgery, which has not been evaluated in this manner before.

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Material and Methods

Patients studied

This prospective study of consecutive patients who submitted to LNF began in 1994 when the primary author (A.C.) had performed this operative procedure in 25 patients as the “learning curve,” which appeared to be adequate, because we have had 20 years of experience performing open fundoplication in a substantial number of patients.^{2,4} All clinical, laboratory, endoscopic, histologic, and functional tests results were recorded in a prospective database. All patients provided their written informed consent to be included in this study. All procedures in human participants were conducted following the Institution and Ministerial Committee and with the 1961 Helsinki declaration and its later amendments or comparable ethical standards. Unique Identifying Registration Number 3743.

Inclusion criteria corresponded to GERD patients with a minimum of 5 years of symptoms, a daily dependence of on proton pump inhibitors (PPIs), and a type-1 hiatal hernia (HH) <5 cm, and whom, after a short suspension of medication, suffered from recurring symptoms.³⁰ This protocol ended in 2003, but the final evaluations were performed in all patients during the years 2017–2018, completing 24–25 years of follow up. Symptom evaluation, Visick score grading, as well as the last endoscopy in addition to biopsy samples were done in these last 2 years. Exclusion criteria included patients with the initial presence of BE, esophageal strictures, failed antireflux surgery before our LNF, patients with obesity (body mass index >30 kg/m²), and HH ≥5 cm. Although the exclusion of the latter 2 groups could be a limitation of our study, patients with HH >5 cm are incorporated in another protocol concerning the use of a mesh, and obese patients were included in a study evaluating the use of gastric bypass.

Radiologic evaluation

This study included 64 patients before their LNF in whom an HH was suspected. Our protocol was established to perform a radiologic evaluation in all patients (100%) 1 month after the LNF to evaluate (at baseline or “0 time”) the anatomic aspect of the fundoplication, emptying of the esophagus (absence of stricture) through a narrow esophagogastric junction (EGJ), and normal gastric emptying. This examination was performed after an overnight fast, using a low-density, barium sulfate suspension (45% weight in volume). Patients usually consumed 200 ml of liquid barium, and 8–10 films were taken in various positions.

Clinical evaluation

A clinical assessment was performed in each patient several times after LNF, always with a “face-to-face” clinical interview and never through indirect means, such as telephone, regular mail, or E-mail. The following parameters were evaluated:

- Heartburn: Graded as absent, occasional (less than once a week), or frequent (more than once a week). Heartburn was defined as a burning sensation in the middle of the chest, which may extend up to the neck and worsens when bending or lying down.
- Regurgitation: Graded similarly to heartburn, was defined as a backward flow of gastric content to the esophagus without any effort.

- Dysphagia: Graded as absent or present, defined as difficulty swallowing.

For a final late clinical evaluation, the modified Visick gradation was employed,^{31,32} because the Visick grading has shown an excellent correlation between symptoms and success or failure of antireflux surgery.³² Visick gradation is as follows:

- Visick I: Asymptomatic, no need for PPIs and normal endoscopy.
- Visick II: The presence of mild or occasional symptoms of heartburn or regurgitation easily controlled with the use of PPIs, with no need for permanent medication. Endoscopic findings corresponded to the presence of type II cardia or the presence of grade A esophagitis without symptoms.
- Visick III: The presence of frequent or daily symptoms controlled only through the permanent daily use of PPIs, endoscopic findings with type III or IV cardia (presence also of an HH), esophagitis grade B or C, or the development of BE.
- Visick IV: The failure of the operation with the presence of severe symptoms that require reoperation to control the recurrent reflux. Endoscopy demonstrating a complete loss of the surgical wrap, the presence of an HH and/or esophagitis C or D, or severe anatomic alterations.

For final clinical analysis, Visick I and II were considered as successes, and grades III or IV were considered as failures of the LNF.

Endoscopic evaluation

All endoscopic procedures were performed by the senior author, employing an Olympus GIFXQ 20 endoscope (Olympus Corp, Tokyo, Japan). After a 12-hour fast and pharyngeal anesthesia with lidocaine, the patient—in a left lateral decubitus—had the endoscope introduced through the mouth. Special care was taken to measure the exact location of the squamous-columnar junction (SCJ) at the beginning and the end, avoiding the “push-and-pull” effects of the endoscope.³³ The presence of erosions proximal to the SCJ was carefully recorded, using the Los Angeles classification.³⁴ The anatomic endoscopic aspect of the EGJ or cardia was determined in 4 grades³⁵ according to the Hill classification, which permits good characterization of the geometry of this area. These findings provide useful information regarding prediction of the reflux status in patients undergoing evaluation for GERD³⁶ before and after any operation. If present, the length of the columnar-lined mucosa was measured from the EGJ to its most proximal limit. To visualize the anatomy of the gastroesophageal flap or cardia, the stomach must be insufflated and the endoscope placed in a retroflexed position, maintaining the vision of the valve during all phases of respiration.³⁷ The findings are divided into the following 4 grades:

- Grade I. The ridge of the tissue at the valve is approximated closely to the shaft of the retroflexed scope.
- Grade II. The ridge is less well defined and it rarely opens with respiration and closes promptly.
- Grade III. The ridge is rarely present, and it fails to close around the endoscope
- Grade IV: No muscular ridge exists. The EGJ stays open all time, and an HH is always present.

For final endoscopic analysis, cardia types I–II were considered a success and grades III–IV were considered a failure of operation and recurrence of reflux.

Histologic analysis

During all endoscopic procedures, biopsy samples were taken from two areas:

- Antrum, taking 2 samples to determine the presence of *Helicobacter pylori*.
- At 5-mm distal to the SCJ, which was referred to as the “juxtacardial zone” (JCZ), taking 3 samples to determine the type of mucosa lining the distal esophagus. If a short segment of a columnar-lined esophagus was suspected, 4 quadrant biopsy specimens were taken.

All samples were submerged immediately in a 10% formalin solution and sent for histologic examinations. Slides were stained with hematoxylin-eosin stain and with Alcian blue at pH 2.5 to search for the presence of intestinal metaplasia (IM).

An expert pathologist in gastrointestinal diseases carefully examined the following three types of epithelium:

- Fundic mucosa was characterized by the presence of parietal cells and chief cells at the deep glandular layer.
- Cardiac mucosa was defined as the presence of mucus-secreting columnar cells. If chronic inflammatory cells were present, the mucosa was defined as “funditis” or “carditis.”
- Specialized columnar epithelium was characterized by the presence of IM with well-defined goblet cells.

These samples were taken before and after LNF in each endoscopic examination. Progression was defined as the change of fundic mucosa to cardiac mucosa or IM. Regression was defined as the change of cardiac mucosa to fundic mucosa.

Manometric studies

Standard manometric testing was carried out with the patient in a left lateral position after a 12-h fast. The complete details of this procedure have been explained elsewhere.^{33,38} The resting pressure and the abdominal length of the lower esophageal sphincter (LES) were measured. The amplitude of the distal esophageal contractile waves was also determined. This examination was always conducted before pH monitoring.

24-hour pH monitoring

This test was performed after a 12-hour fast, introducing the catheter through the nose into the stomach^{39,40} after stopping PPIs for the 6 days preceding the test. The tip of the catheter was placed 5-cm proximal to the upper border of the LES. Among the 6 parameters that can be evaluated, the most practical and useful score is the total percentage of time in which the intraesophageal pH remains <4 throughout the 24 hours, with a standard abnormal value considered below 4%. We always prefer this score to the DeMeester score, because this score of a duration of abnormal pH is easier to understand and remember. Both manometry and 24-hour pH monitoring tests were performed 3 to 5 years after the operation.

Surgical procedure

All patients were submitted to LNF according to our technique published elsewhere.^{41,42} Four main steps we believe to be essential: (1) Careful dissection of the distal esophagus, EGJ and a portion of the fundus, always transecting the first two short gastric vessels, which correspond to the vessels coming from the posterior fundus

to the retroperitoneum. On occasion, we also transect the proximal short gastric vessels from the spleen to the greater curvature. The anterior branch of the vagus nerve is preserved during the dissection of the EGJ similar to what we did during highly selective vagotomy. If the patient has had a cholecystectomy, the hepatic branch can be divided. The posterior branch of the vagus, which runs closely along the right crus must be visualized and preserved so that the patients does not experience diarrhea or gastroparesis after the LNF. (2) Closure of the hiatus behind the esophagus with 2 to 3 stitches of 0 silk according to the defect. (3) A 360° symmetric fundoplication, 4 cm in length, employing 4 stitches of 2-0 silk, using a 42-Fr calibration bougie. (4) Anterior fundophrenopexy with 2 stitches of 2-0 silk. Afterward, the bougie is removed carefully and then reintroduced into the stomach to relieve any excessive tension or stricture caused by the fundoplication stitches.

Patients had no intake of liquid for 24 hours. They only received water orally on day one and a liquid diet subsequently. In this way, we were able to evaluate the presence of dysphagia. This diet was modified 1 month postoperatively when a radiologic evaluation was performed in all patients (baseline evaluation).

Follow-up

All patients were followed up 1 month and 1 year after surgery and then every 3–5 years.

Statistical analysis

For calculation of statistical significance, the χ^2 test and the Fisher exact test were used, with $P < .05$ considered statistically significant. All values are expressed as a mean \pm standard deviation

Results

Clinical outcome

We included 179 patients in this prospective study consisting of 69 men and 110 women with a mean age of 44 years (range 20–77 years). There was no operative mortality.⁴² Two patients had mild complications, and there were no conversions to an open operation. The average hospital stay for these 177, noncomplicated patients was 2.7 days. None of the patients had dysphagia with the liquid diet during the first month postoperatively, and none required endoscopic dilatation. The [Figure](#) presents the patient flow diagram of the late results after LNF. Four patients (2.2%) died 3 to 4 years after LNF because of pancreatic cancer, lung cancer, myocardial infarction, and a car accident. A total of 25 (14%) were lost to follow-up: 6 with no follow-up, 3 with less than 24 months' follow-up, and 16 with 36 to 84 months' follow-up. Therefore, 150 patients (83.8%) were included in the final results of this study. This [figure](#) also shows the final clinical evaluation according to Visick grade, with a mean follow-up of 15 years and a range of 12–24 years. At the first formal evaluation 15 months postoperatively, 98% of patients were asymptomatic. The mean time to recurrence of symptoms and daily dependence on PPIs corresponded to 74 \pm 22 months (Visick III). The distribution of Visick grading according to the sex of the patients was similar. In women Visick I-II versus III-IV was 79% vs 21% and in men Visick I-II versus III-IV was 88% vs 12%. The mean age for Visick I-II versus Visick III-IV for female patients was no different 48 \pm 13 years vs 51 \pm 12. The corresponding Visick grades in male patients were 41 \pm 11 vs 43 \pm 12 years.

The total number of objective evaluations before and after LNF are presented in [Table 1](#). All patients underwent endoscopic and functional tests preoperatively. After LNF, a mean of 3.6 upper endoscopies were performed postoperatively per patient at 15 \pm 6

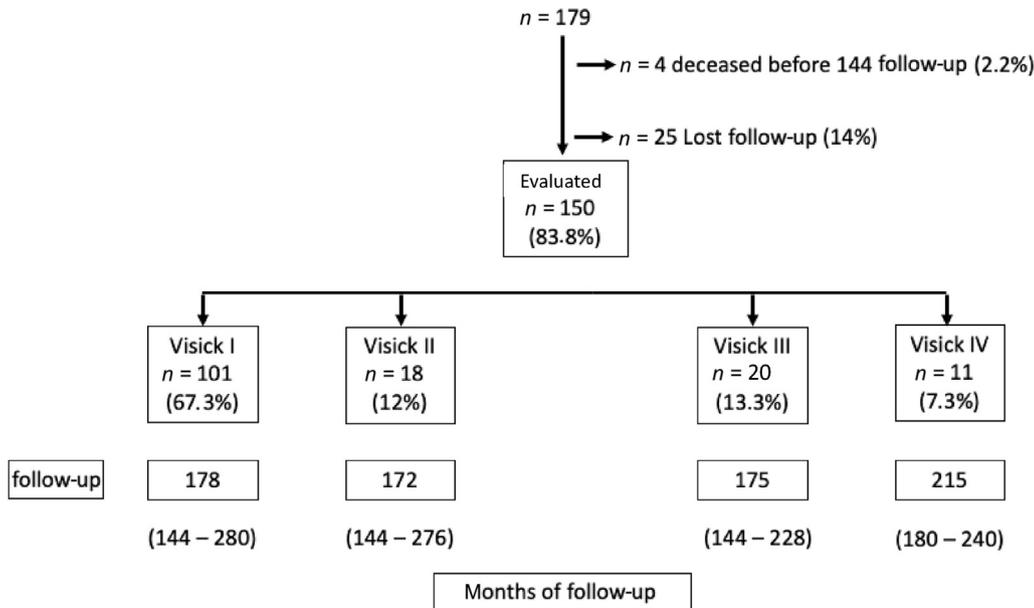


Figure. Patients' flow diagram concerning late follow-up after LNF.

months ($n = 150$), 58 ± 13 months ($n = 120$), 115 ± 12 months ($n = 122$), 156 ± 22 months ($n = 122$), and 229 ± 22 months ($n = 42$). Note that upper endoscopy was performed routinely and was not symptom driven. A mean of 3.4 histologic samples at the JCZ were taken at 58, 115, 156, and 229 months postoperatively. Esophageal manometry plus 24-hour pH monitoring were performed in 105 patients (70%).

Radiologic control evaluation

One month postoperatively, all patients underwent this evaluation. In all, a surgical wrap at EGJ was seen. This examination was repeated in some patients with a recurrence of symptoms to compare it with the baseline study.

Endoscopic evaluation

The endoscopic findings late postoperatively are presented in Table II. All 101 patients with Visick I had normal findings at upper endoscopy, with visualization of a symmetric and geometric flap valve from the retroflexed vision. Of the 18 Visick II patients, 10 had a normal cardia but with some occasional symptoms of reflux, and 8 had erosive grade A esophagitis with a dilated cardia, but no reflux symptoms. A total of 20 patients were classified as Visick III because of the finding of erosive esophagitis grades A, B, or C, in addition to the presence of a type III cardia or the appearance of an HH. Of these patients, 3 were chronic users of corticosteroids, 5 had

developed a short-segment BE, and 2 showed retention of fluid at the distal esophagus during endoscopy, 11 were reoperated and therefore classified as Visick IV, with grade B to D esophagitis.

Histologic analysis

Table II also presents the histologic findings at the EGJ and the antrum before and after surgery. Carditis was the main histologic finding in 73% of patients preoperatively. After the operation, there was significant regression to a normal fundic mucosa ($P < .01$). Individual analysis of the histologic changes demonstrated that, postoperatively, the most frequent change corresponded to regression from carditis to fundic mucosa (52 cases), and progression of fundic mucosa to carditis occurred in 10 patients. The development of BE was observed in 8 patients (5.3%) as presented in Table III, with a mean length of the columnar-lined mucosa of 22 mm. This histologic change occurred in 7 women and 1 man at a mean of 13 years (9–20 years) postoperatively, 2 of whom were

Table I
Objective evaluations before and after laparoscopic Nissen fundoplication

Parameters	Before LNF $n = 179$	After LNF $n = 150$
Radiology	86 (48%)	150 (100%)
Upper endoscopy	179 (100%)	540 (3.6/pt)
Histology EGJ	537 (100%)	1,852 (3.4/ex/pt)
Manometry	179 (100%)	105(70%)
24-h pH monitoring	179 (100%)	105 (70%)

pt, patient; ex, examination.

Table II
Endoscopic and histologic findings before and after LNF

Parameters	Before LNF $n = 179$		After LNF $n = 150$			
			Visick I-II $n = 119$		Visick III-IV $n = 31$	
				<i>P</i> value		<i>P</i> value
Endoscopic findings						
Esophagitis A	67 (37.4%)	8 (6.7%)	.001	8 (26%)	ns	
Esophagitis B–C	20 (11.2%)	0	—	14 (32%)	<.0002	
Cardia type I–II	2	111 (91.7%)	<.05	2	<.04	
Type III	113 (63.1%)	8 (6.7%)	<.05	10 (32%)	<.001	
Type IV	64 (35.7%)	0	—	19 (61%)	<.007	
Histologic findings						
Juxtacardial area						
fundic mucosa	48 (26.8%)	72 (60.5%)	<.05	4 (13%)	ns	
carditis	131 (73.2%)	47 (39.5%)	<.05	19 (61%)	ns	
intestinal metaplasia	0	0	—	8 (26%)	—	
Antrum						
<i>H. pylori</i> (+)	44 (24.6%)	9 (7.5%)	<.002	3 (10%)	ns	

ns, not significant.

Table III
Development of intestinal metaplasia at the distal esophagus after LNF

Case	Age (y)	Sex	Preoperative histology	Preoperative studies		Postoperative studies		Development IM	
				LESP	pH	LESP	pH	months	Visick
1	43	M	Carditis	5	4	15	<1	120	III
2	48	F	Carditis	8	8	12	4	108	III
3	49	F	Carditis	3	21	7	7	156	III
4*	48	F	Carditis	5	8	7	8	180	III
5*	57	F	Funditis	10	11	15	9	180	III
6	67	F	Carditis	6	48	8	9	108	IV
7†	45	F	Carditis	7	23	12	1	240	IV
8	38	F	Carditis	3	33	8	14	144	IV

M, male; F, female; LESP, lower esophageal sphincter pressure (mmHg); pH, percentage of time with pH <4 in 24 h.

* Chronic use of steroids.

† Development of early adenocarcinoma (reoperated).

chronic users of corticosteroids, and 24-hour pH monitoring was abnormal in 6. One patient developed an early adenocarcinoma. The presence of *H. pylori* preoperatively was observed in 25% of the patients, and eradication therapy was administered in all. At late evaluation, *H. pylori* was found in 12 patients (8%).

Functional studies

The results of manometric and 24-hour pH tests before and 3 to 5 years postoperatively are presented in Table IV. They are separated into the following 2 groups: success (Visick I-II) or failure of the operation (Visick III-IV). Visick I-II patients showed a significant increase in resting LES pressure as well as in the abdominal length of the LES ($P < .0001$) and a significant decrease in acid reflux into the esophagus ($P < .0001$). In contrast, although Visick III-IV patients exhibited an increase in resting LES pressure ($P < .001$), there was no change in the presence of abnormal acid reflux ($P > .29$).

Reoperations

Table V presents the functional and endoscopic findings in 11 patients submitted to reoperation. The mean time to reoperation after LNF was 7.7 years (2–15 years). The amplitude of the distal esophageal waves increased significantly in Visick I-II, but showed no change among Visick III-IV patients. A total of 7 patients presented with severe symptoms of GERD plus erosive esophagitis grade B to D, a dilated type III cardia, and an incomplete or defective wrap during retroflexion, which was associated with persistent acid reflux into the esophagus. A total of 4 of these 7 patients showed an increase in pathologic acid reflux, and 3 had less reflux than preoperatively but still within a pathologic range. Patient #8

with gastric lymphoma also showed a pathologic acid reflux test and was converted to total gastrectomy. Patient #9 was asymptomatic until 20 years postoperatively when she presented heartburn and mild dysphagia. Preoperative endoscopy showed X BE. Endoscopy showed a 20-mm long columnar-lined mucosa with an intestinal-type mucosal adenocarcinoma in short-segment BE. The 24-hour pH monitoring was performed 7 years postoperatively. Although she was asymptomatic (13 years before she developed symptoms), the test results were normal. She was first submitted to an endoscopic mucosectomy, but histology demonstrated positive margins, and therefore, she underwent a D2 total gastrectomy with uneventful recovery. Patient #10 developed a stricture at the EGJ and was reoperated 2 years postoperatively. Patient #11, who developed a BE 12 years postoperatively and X have BE preoperatively, also had an HH of 4 cm and esophagitis grade C. The reoperative surgery in patients #1 to #7 and #11 consisted of refundoplication plus partial gastrectomy and Roux-en-Y reconstruction with a 70- to 80-cm long limb to avoid bile reflux, as has been our policy in these cases.⁴³

Discussion

The results of the present prospective investigation suggest some unique features that can be summarized as follows:

- All patients were submitted to several endoscopic evaluations (a mean of 3.6 per patient) at various time periods postoperatively.
- The results of the histologic analysis at the EGJ and the antrum are reported for the first time before and several times postoperatively.
- In addition to symptom evaluation, functional studies measuring the antireflux effect of the LNF were performed in 70% of the patients postoperatively.
- Development of short-segment BE was demonstrated in 5.3% at a mean of 13 years postoperatively.
- Late follow-up evaluation at a mean of 15 years (range 12–24 years) was completed in 83% of the patients included in this study

The 3 ways to evaluate the late results of antireflux surgery are as follows: symptom evaluation, upper endoscopy plus biopsy samples, and functional studies (manometry and 24-hour pH monitoring). In our study, we used the Visick gradation for clinical evaluation, which has shown a perfect correlation between the presence of symptoms and the success or failure of the operation.³² This system is much more precise than terms used in several reports, such as “well, good or bad” results, also showing a close correlation with endoscopic findings. We have not used the quality-

Table IV
Esophageal manometry and 24-h pH monitoring before and late after LNF

Parameters	Before LNF (n = 179)	After LNF (n = 105)				
		Visick I-II n = 77	Visick III-IV n = 28	I - II versus III - IV P value		
Manometry						
LESP (mmHg)	8 ± 3	14.2 ± 3.7	.0001	11 ± 5	.0001	ns
Abdominal length (mm)	4 ± 4	12.0 ± 5.5	.0001	8 ± 4	.0001	.01
Distal waves (mmHg)	58 ± 30	65.1 ± 32.4	.0001	58 ± 34	ns	.001
24-h monitoring						
percentage time pH < 4	19 ± 6	2 ± 2	.001	17 ± 17	ns	.001
number of patients pH < 4 %	0	69 (90%)	—	2 (8%)	—	—

LESP, lower esophageal sphincter pressure; ns, not significant.

Table V
Objective evaluations in patients undergoing reoperative antireflux surgery after a failed LNF

Case	Time to redo antireflux operation (y)	Preoperative studies			Postoperative studies			
		LESP	AL	pH	LESP	AL	pH	Endoscopic findings
1	15	7	5	13	14	5	5	B
2	8	4	0	28	7	5	32	C
3	6	23	0	41	10	10	16	C
4	2	16	10	24	6	5	11	D
5	9	10	0	5	19	10	19	D
6	3	6	0	4	7	5	9	B
7	11	10	0	5	19	10	18	C
8	8	6	10	28	8	5	9	GL
9	20	7	10	23	12	12	1	BE-AdC
10	4	7	10	26	15	10	32	SEGJ
11	14	3	10	33	8	10	14	BE

LESP, lower esophageal sphincter pressure (mmHg); pH, percentage of time with pH < 4 in 24 h; AL, abdominal length of LESP (mm); GL, gastric lymphoma; AdC, adenocarcinoma; SEGJ, stenosis esophagogastric junction.

of-life system for symptom evaluation in any of our earlier reports. It is well known that complete elimination of reflux symptoms does not guarantee normalization of intraesophageal pH,⁴⁴ as shown in our 8. Asymptomatic, Visick II patients who presented grade A esophagitis. In contrast, we have observed that the patients who require the daily use of PPIs always correspond to reflux recurrence, contrary to what has been published before by other authors,^{45,46} who have suggested that only 30% of patients dependent on PPIs indeed had actual reflux.

When analyzing the literature concerning the late results of LNF, we found 19 publications that reported this topic.^{10,12–29} A total of 10 (53%) used only symptomatic evaluations, endoscopic or functional studies were performed in a low number of patients in 6 (32%) of these reports, and only 11 (58%) discuss a follow-up in more than 80% of the patients.

The presence of heartburn late after LNF is not even discussed in 3 reports, and 11 reports (58%) discuss the presence of heartburn in more than 20% of the patients, with more than 40% in 3 publications. This is consistent with the daily use of PPIs in more than 20% of the patients in 10 publications.

As discussed, endoscopy is an excellent objective method for determining success or failure of the operation. It can visualize the distal esophagus for esophagitis, columnar-lined esophagus, or recurrent HH, and on retroflexion can evaluate the anatomic aspect of the wrap. There is a good correlation between this latter finding, and the success or failure after antireflux surgery as was demonstrated by Jobe et al³⁶ and Salminen et al.²⁰ This is why we

Table VI
Endoscopic findings before and after LNF

Authors	Preoperative findings		Postoperative findings	
	n	Results	n	Results
Fein et al (2008) ¹⁸	85	Esophagitis 59% HH 57%	48 (56%)	Esophagitis 4% HH 6%
Neuvonen et al (2014) ²⁴	107	—	64 (60%)	Surgical failure (12%)
Salminen et al (2012) ²⁰	44	—	38 (90%)	HH (31%) BE (19%)
Schietroma et al (2013) ²¹	118	Esophagitis 51,2%	—	Esophagitis (7.8%)
Djerf et al (2015) ²⁵	36	Esophagitis 22%	12 (33%)	all 12 normal
Ribeiro et al (2016) ²⁸	32	—	—	Esophagitis (42%)
Csendes (2019) (present study)	174	Esophagitis (48%) HH (36%)	150 (80%)	Esophagitis (20%) HH (12.6%) BE (5.3%)

performed several endoscopic examinations postoperatively at different times.

Table VI presents 6 studies reporting some endoscopic findings postoperatively. It is remarkable that only one examination reported in 33%–90% of the patients, with the report of Salminen et al.²⁰ being the most complete. Endoscopy was performed in 90% of their group of 44 patients, describing the appearance of esophagitis and HH late after surgery in 30% of the patients, plus the development of BE in 19%, being the only authors to discuss this complication. It can be observed that 3 out of 6 publications report endoscopic failures at greater rates than the value determined by symptomatic evaluations discussed in the 10 publications without objective measurements.

One of the unique aspects of our study that has not been evaluated or discussed elsewhere corresponds to the multiple biopsy samples taken at the JCZ, which is the only objective way to prove the development of BE after antireflux surgery. The endoscopic appearance of a columnar-lined distal esophagus may correspond only to carditis, which is an excellent marker for the presence of chronic GERD⁴⁷; however, the diagnosis of BE is based on the presence of IM and goblet cells.⁴⁸ In our study, we showed the development of BE in 5.3% of patients, but this progression from carditis to IM takes a mean time of 13 years. The importance of this finding is that, if biopsy samples are taken 5–10 years postoperatively, the presence of BE may not be diagnosed. Concerning the development of BE after antireflux surgery, we have addressed this topic before.⁴⁹ Several authors, such as DeMeester,⁵⁰ Theisen and Oberg,⁵¹ Gutschow et al,⁵² and Wetscher et al,⁵³ have postulated that development of BE is exceedingly rare in patients who have an effective antireflux operation, and no reports have been published concerning this topic. In our report, however, we have commented on 12 patients submitted to open (9) or laparoscopic (3) antireflux surgery who were followed for 12 years, demonstrating that performing 5.2 endoscopies per patient after surgery, the appearance of IM occurred 8 years after operation, with a length of columnar-lined mucosa of 18 mm. A total of 4 of these patients had no absence of pathologic reflux, and 8 had abnormal acid reflux. One explanation of our finding could be that not only acid but also duodenal content can be present in the refluxate to the distal esophagus in the absence of acid reflux. A total of 6 of these patients also had a Bilitec test, which measures bile reflux with positive results in 3 (50%) of them. Furthermore, we have found 5 more publications with more than a 5 year follow-up, describing the development of BE after antireflux surgery, discussing this particular point in 9%–12% of patients with an intact wrap and 23%–33% with a defective wrap.^{7,54–57}

The other new finding of our study is the regression of carditis to fundic mucosa in Visick I-II patients, which again is an objective measurement of a successful antireflux surgery. As a conclusion of our measurements, we postulate that endoscopy plus biopsy samples should be part of the protocol for routine postoperative surveillance and based not only on a symptoms-driven analysis.

Another vital way to control the success or failure of antireflux surgery is through the performance of functional studies, such as an esophageal manometry plus 24-hour pH monitoring. These examinations are more difficult to perform postoperatively, especially in asymptomatic patients. We have shown that there is an excellent correlation between 24-hour pH monitoring and Visick grading, much better than the determination of the pressure in the LES after surgery. As presented in Table IV, Visick I-II as well as Visick III-IV patients showed an increase of LES pressure after LNF, despite the persistence of pathologic acid reflux in the latter group. We can postulate at least 2 explanations for this observation. First, manometric studies were performed 3–5 years postoperatively when the majority of patients were asymptomatic, and the final Visick

Table VII
24-h pH monitoring before and after LNF

Authors	Preoperative values		Post-operative values	
	n	pH	n	pH
Fein et al (2008) ¹⁸	85	DM 46	48 (56%)	10%
Broeders et al (2009) ¹⁹	79	Unknown	10 (13%)	30% abnormal reflux
Broeders et al (2013) ²³	53	Unknown	10 (19%)	3% reflux
Schietroma et al (2013) ²¹	118	18%	Unknown	0.5% reflux
Djerf et al (2015) ²⁵	36	9%	12 (33%)	All 12 normal
Ribeiro et al (2016) ²⁸	32	Unknown	Unknown	20% abnormal reflux
Csendes (2019) (present study)	179	18.5%	80	Visick I-II (2.1%)
		HH (36.8%)	25	Visick III - IV (16.7%) BE (5.3%)

DM, DeMeester score; pH, % of time with pH <4 in 24 h.

gradation was done at a mean of 15 years postoperatively. In one of our earlier prospective randomized studies comparing 2 types of fundoplication,² we performed several manometric studies up to 10 years postoperatively and found that, among patients with failure of the operation, the “early” increase (1–3 years postoperatively) in LES pressures decreased to near preoperative values “late (10 years)” postoperatively. And second, we did not measure the spontaneous sphincter relaxations in patients with normal resting pressure, which is a frequent finding in patients without reflux, which explains the pathologic acid reflux in GERD patients.⁵⁸

The postoperative manometric evaluations also demonstrated a significant increase in the amplitude of the distal esophageal waves after LNF, regardless of whether there was defective peristalsis preoperatively. It is essential to exclude motor disorders, such as scleroderma or achalasia, and we believe that it is mandatory to perform a manometry in every patient candidate for operative treatment.

Table VII demonstrates the 24-hour pH monitoring described in patients after LNF. This examination was also performed by 6 authors but in a lesser number of patients than endoscopic procedures (12%–56% of operated patients). It is difficult to understand the reports of Broeders et al^{19,23} who in the first report described 30% of pathologic acid reflux after fundoplication and 4 years later only 2.8% of patients. In the same way, Djerf et al²⁵ evaluated only 12 of the original 36 patients after fundoplication (33%), finding normal values in all. Our study demonstrated normal acid values among Visick I and II patients, but persistent acid reflux was observed in patients with failure of the operation (Visick III-IV).

What is considered the optimal technique for Nissen fundoplication? Nissen himself published in 1956⁵⁹ the main 3 steps during the operation: (1) mobilization and dissection of the distal esophagus and EGJ, (2) mobilization of the greater curvature of the stomach, and (3) approximation of the posterior wall of the stomach to the anterior wall behind the esophagus and suturing them in front of it, thereby creating a wrap 3–6 cm long. Later, the transection of the short gastric vessels was added⁶⁰ for many reasons, involving a decrease in the tension of the fundus, which envelops the esophagus, avoiding a “twist” of the esophagus, and facilitating the dissection of the posterior portion of the EGJ and the pillars of the diaphragm. Concerning this point, we are aware of the randomized studies^{12,15,17,29} that have questioned the need for transection of the short vessels; however, it is not explained clearly which short vessels are transected. In our experience of antireflux surgery as well as highly selective vagotomy and gastrectomies for ulcer and cancer, we have observed that the first 2 short vessels run from the posterior part of the fundus to the retroperitoneum, thereby maintaining this portion of the stomach fixed and thus making their transection imperative to obtain a “floppy” Nissen, which is our technique. If the authors refer only to the transection

of the short gastric vessels from the spleen to the fundus or greater curvature, then under this circumstance it is not necessary to transect them. From the 19 reports concerning LNF, 12 (63%), routinely perform division of the short gastric vessels, just as we did.

We have never performed partial fundoplication types (Toupet or Lind) in our patients, because the literature reports conflicting results after these procedures, and especially with several reports discussing a high incidence of recurrent reflux after these partial fundoplications.^{61–63} In the same way, we have not performed a “tailored” approach in GERD patients who are candidates for surgery in whom preoperative manometry demonstrates ineffective peristalsis. We maintain that the available evidence, although controversial, suggests that the outcome of patients with esophageal dysmotility is not affected by the type of fundoplication.^{64–66}

The importance of our study is to demonstrate that the correct scientific way to evaluate and follow a patient with GERD submitted to LNF is: (1) to perform a careful clinical analysis of symptoms based on individual face-to-face evaluations and not through indirect means such as telephone or E-mail; (2) that endoscopic evaluation both preoperatively and postoperatively is essential to determine the anatomy of the wrap, the aspect of the distal esophagus, and the presence or not of a dilated cardia; (3) endoscopic examination must be complemented by taking biopsy samples, which is the only way to demonstrate the histologic appearance at the EGJ and the progression or regression of histologic changes, because these changes may occur late postoperatively (at a mean of 13 years) as observed in our results; and (4) if possible, functional studies, which are the best way to prove the antireflux effect of antireflux surgery, should be done on several occasions postoperatively.

The strengths of our study are: (1) it is a prospective evaluation of a large number of patients; (2) the follow-up takes place over an extended period of time, with a mean of 15 years; (3) more than 80% of the original group has been followed-up clinically; and (4) several objective evaluations were performed multiple times postoperatively.

The weaknesses of our study are: (1) it is not a randomized protocol; (2) it was performed by a small group of surgeons; and (3) because this report comprises long-term data, which collects patients from our early experience concerning a long time span (24 years), the learning curve could have some influence on the results. For that reason, we performed the first 25 fundoplications without including them in the present evaluation.

In conclusion, LNF is an effective, longstanding, antireflux operation in a minimum of 79% of patients. Consecutive objective measurements have demonstrated the development of BE in 5% late after LNF (mean of 13 years), and 1 patient even developed an esophageal adenocarcinoma 20 years after LNF. We firmly believe that surgeons dedicated to this area should include in their reports not only clinical analysis but also essential evaluations of the antireflux effect of this antireflux surgery.

Conflict of interest

The authors declare they do not have relevant, material, or financial interests that relate to the research described in this article.

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