

PERTTU NEUVONEN

Long-term Results of Nissen Fundoplication

The background of the cover is white, featuring a decorative pattern of numerous translucent blue spheres of varying sizes. These spheres are scattered across the page, with some appearing larger and more prominent than others, creating a sense of depth and movement. The spheres have a slightly textured, mottled appearance, giving them a three-dimensional quality.



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of Nissen Fundoplication



ACADEMIC DISSERTATION

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UNIVERSITY OF TAMPERE

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ACADEMIC DISSERTATION

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ABSTRACT

Gastroesophageal reflux disease has become the most common gastrointestinal disorder in the Western world. The currently prevailing surgical treatment, Nissen fundoplication, was originally developed in 1955, and the laparoscopic technique was utilized for the first time in 1991. There are few pragmatic studies presenting long-term results of laparoscopic Nissen fundoplication from routine clinical practice, and even though the treatment method is 60 years old, the longest follow-up studies are limited to 20 years.

This thesis consists of four independent articles. The aim of our first study (I) was to describe the indications, operative technique, and annual rates of antireflux surgery at Kanta-Häme Central Hospital after the dissemination of the laparoscopic technique. The results showed that, after the introduction of the laparoscopic technique, the number of antireflux operations rose markedly. Although only patients with objectively verified GERD were treated, the rise in the operation rates was considered to be a result of the broadening of the indications to include a wider range of patients. The operative technique became more standardized towards the end of the 1990s.

Our second (II) and third (III) articles concerned the long-term results of laparoscopic Nissen fundoplication at Kanta-Häme Central Hospital. In our second study (II), the aim was to define the ten-year results as regards the health-related quality of life of our patient cohort. The objective of our third study (III) was to describe the long-term durability of surgical results in routine clinical practice, the impact of fibrin glue on the incidence of surgical failure, and the subjective outcomes ten years after the operation. We found that the health-related quality of life of the patient cohort was close to that of the Finnish general population. The patient satisfaction was high, but dissatisfaction with the treatment was associated with the decreased health-related quality of life. Flatulence and dysphagia were the most common side effects of the treatment, while dysphagia was the most common problem among the dissatisfied. Eighty-nine percent of the fundoplication wraps were intact, and only 6% of the patients were unsatisfied with the results. The subjective and objective long-term results were comparable to those published from more specialized centers. For the first time, it was noted that the use of fibrin glue seemed to decrease the incidence of defective fundoplication wraps in the long term.

In our fourth (IV) article, we aimed to present almost lifelong follow-up (>30 years) after open Nissen fundoplication in terms of subjective outcomes and health-related quality of life and to describe the indications for antireflux surgery before the laparoscopic era. According to our results, a successful Nissen fundoplication may provide a lifelong control

of reflux symptoms, and the health-related quality of life of the patients was comparable to that of the general population over 30 years after the operation. The indications for the procedure reflected the practices of the time, and, in most of the patients, GERD was objectively verified.

The results of this thesis suggest that laparoscopic Nissen fundoplication can provide durable surgical results in routine clinical practice as well. In the case of successful surgery, fundoplication may give the patient a lifelong relief of reflux symptoms, but the potential risks and treatment-related side effects should be weighed cautiously when considering operative treatment. These results provide information for physicians and patients when weighing the benefits and harms of the treatment.

TIIVISTELMÄ

Refluksitaudista on tullut yleisin mahasuolikanavan sairaus länsimaissa. Tällä hetkellä valtamenetelmänä oleva kirurginen hoito, Nissenin fundoplikaatio, kehitettiin alun perin vuonna 1955, ja ensimmäinen tähystysavusteinen fundoplikaatio tehtiin vuonna 1991. Vaikka leikkausmenetelmä on jo 60 vuotta vanha, pitkäaikaistuloksia, jotka kuvaavat menetelmän käyttöä valikoimattomissa potilasaineistoissa, on julkaistu vähän. Pisimmät seurantatutkimukset rajoittuvat ylipäätään 20 vuoteen.

Tämä väitöskirjatyö koostuu neljästä vertaisarvioidusta alkuperäisartikkelista. Ensimmäisessä osatyössä (I) tavoitteemme oli kuvata leikkaushoidon aiheet, leikkaustekniikka sekä vuotuiset leikkausmäärät Kanta-Hämeen keskussairaalassa tähystysavusteisen leikkaustekniikan käyttöönoton jälkeen. Tuloksiemme mukaan leikkausmäärät lisääntyivät merkittävästi tähystysleikkausten myötä. Vaikka leikkausaiheena oli objektiivisilla tutkimusmenetelmillä todettu refluksitauti, leikkausmäärän kasvamisen katsottiin johtuvan leikkausaiheiden laajenemisesta koskemaan suurempaa potilasjoukkoa. Leikkaustekniikka kehittyi standardoidummaksi 90-luvun loppua kohti.

Toinen (II) ja kolmas (III) osatyömme käsittelivät Kanta-Hämeen keskussairaalassa tähystysavusteisesti fundoplikaatio-leikattujen potilaiden pitkäaikaistuloksia. Toisessa (II) osatyössä tavoitteemme oli määritellä leikkauspotilaiden elämänlaatu kymmenen vuotta leikkauksen jälkeen. Kolmannessa (III) osatyössä halusimme selvittää leikkaustuloksen kestävyyttä valikoimattomassa potilasaineistossa, fibriiniliiman vaikutusta leikkaustulokseen sekä potilaiden oireilua ja tyytyväisyyttä. Tutkimustemme mukaan leikkauspotilaiden elämänlaatu oli lähes vastaava kuin suomalaisella verrokiväestöllä. Suurin osa potilaista oli tyytyväisiä leikkaustulokseen, mutta tyytymättömyys oli yhteydessä alentuneeseen elämänlaatuun. Ilmavaivat ja nielemisvaikeudet olivat yleisimpiä hoitoon liittyviä sivuvaikutuksia, ja nielemisvaikeudet olivat yleisin ongelma tyytymättömillä potilailla. Ehjiksi todettiin 89 % fundoplikaatio-manseteista, ja vain 6 % potilaista ilmoitti olevansa tyytymättömiä leikkaustulokseen. Subjektiiivisten ja objektiivisten tulosten katsottiin olevan vastaavat kuin aiemmin raportoidut, pidemmälle erikoistuneista yksiköistä julkaistut tulokset. Ensimmäistä kertaa fibriiniliiman käytön vaikutus yhdistettiin leikkaustuloksen pettämistä vähentäväksi tekijäksi pitkäaikaisseurannassa.

Neljännessä (IV) osatyössä halusimme selvittää Tampereen yliopistollisessa sairaalassa yli kolmekymmentä vuotta aiemmin avomenetelmällä leikattujen potilaiden subjektiiviset leikkaustulokset, elämänlaadun sekä ennen tähystysaikakautta käytössä olleet leikkausaiheet. Tuloksemme antavat viitteitä siitä, että onnistuneen Nissenin fundoplikaatio

leikkauksen jälkeen potilaat saattavat saada elinikäisen avun refluksoireiluun. Potilaiden elämänlaatu todettiin vastaavaksi kuin suomalaisen verrokkiväestön yli kolmekymmentä vuotta leikkauksen jälkeen. Leikkausaiheiden katsottiin heijastavan 80-luvulla vallinneita käytäntöjä. Suurimmalla osalla potilaista oli objektiivisesti varmistettu refluksoitauti.

Tähystysavusteisella Nissenin fundoplikaatiolla on saavutettavissa kestävä leikkaustulos myös valikoimattomissa potilasaineistoissa. Onnistuneella leikkaustuloksella on mahdollisesti saavutettavissa elinikäinen helpotus refluksoireiluun, mutta leikkaukseen liittyvät potentiaaliset riskit ja sivuvaikutukset on otettava huomioon mietittäessä kirurgista hoitoa hoitovaihtoehtona. Sekä kirurgit että potilaat voivat hyödyntää tämän väitöskirjan tuloksia arvioidessaan hoitoon liittyviä hyötyjä ja haittoja.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by the Roman numerals I–IV:

- I Rantanen T, Neuvonen P, Iivonen M, Tomminen T, Oksala N. The impact of fibrin glue in the prevention of failure after Nissen fundoplication. *Scand J Surg* 2011 100(3): 181-185.
- II Neuvonen P, Iivonen M, Sintonen H, Rantanen T. Health-related quality of life 10 years after laparoscopic Nissen fundoplication—results of a community-based hospital. *J Laparoendosc Adv Surg Tech A* 2014 24(3): 134-138.
- III Neuvonen P, Iivonen M, Rantanen T. Endoscopic evaluation of laparoscopic Nissen fundoplication: 89 % success rate 10 years after surgery. *World J Surg* 2014 38(4): 882-889.
- IV Neuvonen P, Sand J, Matikainen M, Rantanen T. Does Nissen Fundoplication Provide Lifelong Reflux Control? Symptomatic outcome after 31–33 Years. In Press, *World J Surg* 2017.

ABBREVIATIONS

AGA	American Gastroenterological Association
CT	computer tomography
EAC	esophageal adenocarcinoma
BE	Barrett's esophagus
ERD	erosive reflux disease
GEJ	gastroesophageal junction
GERD	gastroesophageal reflux disease
GERD-HRQL	Gastroesophageal Reflux Disease – Health-Related Quality of Life
GSRS	Gastrointestinal Symptom Rating Scale
HRQoL	health-related quality of life
IM	intestinal metaplasia
LA	Los Angeles
LAF	laparoscopic partial anterior fundoplication
LES	lower esophageal sphincter
LNF	laparoscopic Nissen fundoplication
LTF	laparoscopic Toupet fundoplication
MII-pH	multichannel intraluminal impedance pH monitoring
NERD	non-erosive reflux disease
ONF	open Nissen fundoplication
PPI	proton pump inhibitor
RCT	randomized controlled trial
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SGVs	short gastric vessels
SAP	symptom association probability
SI	symptom index
SSI	symptom sensitivity index
VAS	visual analogue scale

1 INTRODUCTION

Gastroesophageal reflux disease (GERD) causes a notable burden on health care resources, as the disease has become the most common gastrointestinal disorder in the Western world (Peery et al. 2015). Approximately 10%–30% of people report weekly symptoms (Diaz-Rubio et al. 2004; El-Serag et al. 2004; Isolauri and Laippala 1995; Ronkainen et al. 2005b). The two main treatment alternatives for GERD are medical and surgical treatment.

The prevailing surgical treatment, Nissen fundoplication, was originally discovered in 1955 by Rudolph Nissen (Nissen 1956a). The less-invasive laparoscopic technique was introduced in 1991 (Dallemaigne et al. 1991). The laparoscopic approach has since established a position as the gold standard for antireflux surgery, and the number of antireflux procedures multiplied in many countries after the dissemination of laparoscopic Nissen fundoplication (LNF) during the 1990s (Finks et al. 2006; Rantanen et al. 2008; Sandbu and Sundbom 2010). The reflux control and the amelioration of typical reflux symptoms have been reported to be similar or slightly in favor of LNF in the studies comparing LNF and proton pump inhibitor (PPI) treatment with mid-term follow-up (Anvari et al. 2011; Galmiche et al. 2011; Mehta et al. 2006).

However, there are some treatment-related side effects associated with LNF, as the majority of patients report increased bloating and flatulence, and approximately one third to half of the patients have persistent dysphagia of some degree (Broeders et al. 2009b; Kellokumpu et al. 2013; Morgenthal et al. 2007b; Salminen et al. 2012). In addition, questions concerning the long-term efficacy of the surgical treatment have arisen, since a high number of patients have been reported to reinstate antisecretory medication after LNF (Broeders et al. 2009b; Lodrup et al. 2014; Morgenthal et al. 2007b; Salminen et al. 2012). Even though the number of antireflux procedures has decreased in the 21st century and the majority of GERD patients are treated medically with PPIs (Finks et al. 2006; Sandbu and Sundbom 2010), there is a demand for surgical treatment in carefully selected patients, as a proportion of medically managed patients experience breakthrough symptoms and are not unequivocally satisfied with the PPIs (Chey et al. 2010). The most important indication for antireflux surgery is the failure of medical treatment in patients with objectively verified GERD (Kahrilas et al. 2008; Stefanidis et al. 2010; Zerbib et al. 2013).

The long-term results of Nissen fundoplication are needed to enable the patients, who usually seek improvement in their quality of life, as well as the operating surgeons to weigh the benefits and harms of the treatment which irreversibly alters the anatomy of the gastroesophageal junction (GEJ). Most of the studies reporting results of antireflux

surgery are from highly specialized centers, but a significant proportion of the operations are performed at the general level in smaller hospitals (Sandbu et al. 2002; Varban et al. 2011; Viljakka et al. 1997).

This study depicts the long-term results of LNF in routine clinical practice and the results of Nissen fundoplication with a follow-up of more than 30 years. The effect of the wide-scale adoption of the laparoscopic technique is assessed in light of the indications and operation rates.

2 REVIEW OF THE LITERATURE

2.1 The history of reflux disease

“I hope that the memoir will be useful to the future student of Diaphragmatic Hernia, but the examination of it can never afford any one a tithe of the pleasure or profit the original preparation of it afforded me,” stated Henry I. Bowditch in his 1853 monography in which he reviewed contemporary knowledge about hiatal hernia. He went through all the 88 cases of hiatal hernia published in the medical literature between 1610–1846 (Bowditch 1853). The diagnosis of hiatal hernia advanced in the x-ray era. In 1900 Hirsch diagnosed a hiatal hernia using x-rays and a mercury-filled balloon prior to autopsy. In 1904 Eppinger diagnosed a hiatal hernia for the first time in a live patient (Schwarz 1967). In 1926 Åkerlund proposed the term hiatus hernia instead of diaphragmatic hernia and subdivided hiatal hernias into three distinct types: 1) hernias with a shortened esophagus (sliding hernia), 2) paraesophageal hernias, and 3) hernias not included in 1 and 2 (Åkerlund et al. 1926). Rokitsansky was the first to suggest in 1855 that gastric juice may cause inflammation of the lower esophagus (Nissen 1981), but the assumption was not confirmed until 1935 by Asher Winklestein, who defined reflux esophagitis clinically (Winklestein 1935). Philip Allison came to the conclusion that esophageal peptic ulcers were caused by hiatal hernias, because the hernias allowed acid gastric juice to flow in to the esophagus (Allison 1946). The term reflux esophagitis was introduced in 1950 by Norman Barrett, who also noted that it was a common condition and contemplated that strictures in the lower part of the esophagus were of gastric origin (Barrett 1950). For years, the inflammation and strictures of the lower esophagus were considered to be a result of abnormal anatomy of the structures surrounding the paraesophageal junction and, particularly, due to a hiatal hernia. In 1968 Eddie Palmer questioned the relationship between esophagitis and hiatal hernia in a study in which he observed that many patients with hiatal hernias were asymptomatic and, on the other hand, esophagitis could be found in patients without hiatal hernias (Palmer 1968).

2.2 The development of antireflux surgery

The first surgical procedures for GERD were derived from the impression that the pathogenesis was of anatomic and mechanical nature, and hence the surgery focused on hernia repair. In 1919 Soresi published the elective surgical repair of a hiatal hernia.

He described the original abdominal approach to the hiatus. The procedure contained the reduction of the hernia and closure of the opening of the diaphragm (Soresi 1919). In 1950 Sweet published a transthoracic technique in which the hernia was reduced, the phrenic nerve was crushed, and the hernia sac was plicated. In addition, the hiatus was narrowed (Sweet 1950). As the understanding behind the pathogenesis of GERD shifted from the anatomic and mechanical to a functional and physiologic nature, the surgery evolved as well. In 1951 Allison stated that GERD symptoms were related to the abnormal physiology at the cardia and the incompetence of the GEJ was linked to reflux esophagitis. He considered a sliding hernia as the cause of the incompetence. In his transthoracic operative technique, the hiatal reduction was achieved by incising and resuturing the phrenoesophageal ligament and peritoneum to the abdominal aspect of the diaphragm, and the approximation of the diaphragmatic crura behind the esophagus (Allison 1951). Barrett considered the restoration of the cardioesophageal angle the key point in GERD surgery along with hernia reduction. He recommended diminishing the esophageal hiatus when needed (Barrett 1954).

2.2.1 Nissen fundoplication

Fundoplication emerged gradually over the years. In 1936 Rudolph Nissen treated a patient with a distal esophageal ulcer penetrating into the pericardium. In the procedure, he transpleurally resected the distal esophagus and cardia and inserted the esophageal stump into the fundus. In addition, he implanted the distal part of the esophagus into the anterior wall of the gastric body. The patient survived, and the reflux symptoms were noted to have been abolished in the follow-up (Nissen 1937). In 1946 Nissen operated on a colleague suffering from a paraesophageal hernia. He used a transabdominal approach, reduced the hernia, and performed an anterior gastropexy. The patient recovered and became asymptomatic. Nissen thought the success of the procedure was due to the increase in the angle of the His (Nissen 1956b). In 1955 Nissen performed the first fundoplication for reflux esophagitis (Figure 1). He used an abdominal approach, divided the phrenoesophageal ligament, and mobilized the esophagus. The gastric fundus was brought behind the stomach through an opening made by dividing the gastrohepatic ligament. Both the anterior and posterior walls of the stomach were utilized in making a 360-degree fundoplication around the lowest 6 cm of the esophagus. Four or five sutures were used, one or more of which were also fixed to the esophagus. A large-bore intraesophageal stent was used when performing the wrap (Nissen 1956a).

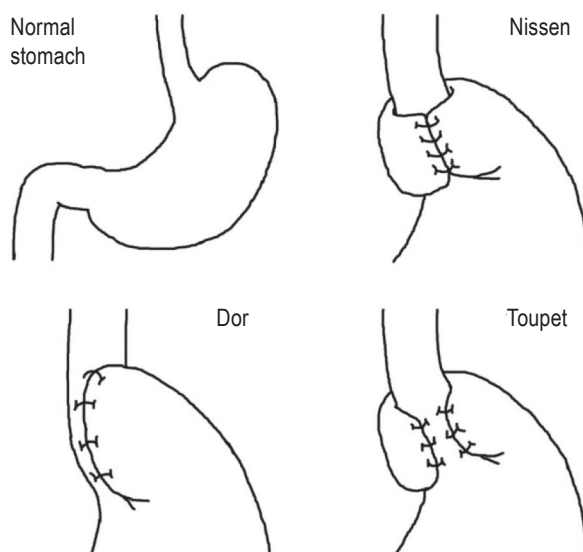


Figure 1. Nissen, Dor, and Toupet funduplications

2.2.2 Modifications of Nissen fundoplication

Since the introduction of the original Nissen fundoplication, many modifications and developments have been created. In 1977 Rossetti, a student of Nissen, published an anterior wall technique, in which a complete loose wrap was achieved by using only the anterior part of the fundus after mobilizing more completely the posterior wall of the stomach from the diaphragm and the left crus. Nissen-Rossetti fundoplication is still commonly applied (Rossetti and Hell 1977). The year 1977 also saw another important technical variation presented, as Donahue described the loosening of the wrap by dividing the upper short gastric vessels (SGVs) along with full mobilization of the posterior fundus and GEJ. The method is known as the floppy Nissen (Donahue et al. 1977). In 1986 DeMeester described a technique in which both posterior and anterior aspects of the fundus were utilized, a routine hiato-plasty was performed, and the SGVs were ligated. A significant development was to shorten the wrap from 4 cm to 1 cm in order to prevent postoperative dysphagia. Also, the caliber of the intraesophageal bougie to calibrate the tightness of the wrap was increased, and teflon felt pledgets were used to strengthen the wrap sutures along with the fixation of the wrap to the esophagus. DeMeester proposed that routine use of the floppy Nissen might improve the postoperative esophageal clearance (DeMeester et al. 1986). The first laparoscopic Nissen fundoplication (LNF) was reported in 1991 by Dallemagne (Dallemagne et al. 1991).

2.2.3 Belsey-Mark IV, Collis gastroplasty, partial funduplications, Hill posterior gastropexy, Roux-en-Y

In the late 1940s, Belsey began to develop antireflux surgery in a series of technical developments. His main idea was to reduce the cardia well below the diaphragm to maintain the cardiophrenic angle and thus secure the competence of the lower esophageal sphincter (LES). After piloting with three different techniques, he adopted the Belsey-Mark IV procedure in 1952. The Belsey-Mark IV is a transthoracic anterior 270-degree partial fundoplication, where the wrap is fixed to the distal esophagus and to the undersurface of the diaphragm. Belsey published the results in 1961 and 1967 only after he had been convinced of the effectiveness of the procedure in the long term (Hiebert and Belsey 1961; Skinner and Belsey 1967). In 1957 Collis published a gastroplasty procedure for irreducible hernias with a short esophagus and strictures (Figure 2). In the procedure, the fundus is incised in line with the esophagus for the proximal part of the lesser curvature to then form the lower part of the esophagus. The technique was recommended especially for the frail and the aged (Collis 1957). The reflux control was not optimal, and complications were linked to the technique, but it was later combined with the Belsey (Pearson et al. 1971) and Nissen operations (Orringer and Sloan 1978). In an effort to minimize the postoperative side effects troubling patients after fundoplication, with dysphagia in particular, partial funduplications have been proposed. In 1962 Dor reported an anterior 180-degree fundoplication in which the wrap covers the anterior aspect of the distal esophagus and is fixed to the edges of the diaphragm (Figure 1) (Dor et al. 1962). In 1963 Toupet described a 270-degree posterior fundoplication (Figure 1). In Toupet's technique, the esophagus and the posterior gastric aspect are mobilized, followed by the anchoring of the left and right sides of the wrap to the anterior wall of the distal esophagus and the edges of the hiatus (Toupet 1963). In 1967 Hill published his posterior gastropexy for an antireflux procedure after analyzing manometry and pH recordings along with cadaver studies. He had come to the conclusion that, in order to restore the angle of His, the phrenoesophageal bundles should be reapproximated and anchored to the median arcuate ligament (Hill 1967). Hill continued his studies on gastroesophageal reflux and, later on, described the gastroesophageal flap valve mechanism (Hill et al. 1996). Roux-en-Y partial gastrectomy with vagotomy has been used in the surgical treatment of severe GERD with esophageal manifestations (Salminen et al. 1997; Salo et al. 1991) and with obese patients (Nadaletto et al. 2016) as well as with reoperations after failed antireflux procedures (Matikainen 1984; Williams et al. 2007).

2.2.4 Recent developments in antireflux procedures

Several less-invasive techniques have been introduced to treat GERD. For the restoration of the function of the antireflux barrier, at least three different gastroscopy-assisted strategies

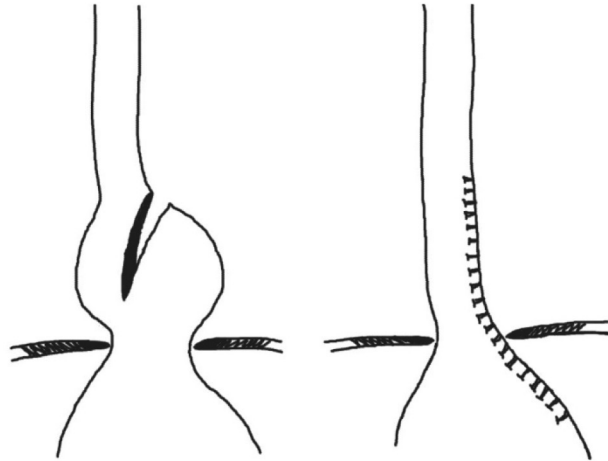


Figure 2. Collis gastroplasty

have been proposed: 1) radiofrequency ablation, in which radiofrequency energy is applied to the GEJ; 2) endoscopic fundoplication, making plication or sutures with commercially available devices; and 3) the insertion of material to the GEJ to form a barrier against reflux. There have been safety, efficacy, and durability issues considering many of the methods, and none of the techniques have surpassed LNF in reflux control (Lo and Mashimo 2015; Pandolfino and Krishnan 2014). Besides the endoluminal techniques, a magnetic sphincter augmentation system has been introduced to restore the competency of the LES. The device consists of a chain of titanium beads, which form a ring that is placed around the esophagus at the level of the LES laparoscopically. Long-term results for the method are not available, and the antireflux efficacy seems poorer than that of LNF (Zak and Rattner 2016).

2.3 Indications for surgery

According to the 2008 medical position statement of the American Gastroenterological Association (AGA), the indication for antireflux surgery is a failure of PPI treatment in patients with objectively verified GERD, especially in the case of persistent difficult regurgitation. Patients with refractory extraesophageal GERD syndromes might also benefit from surgery, when the reflux causality has been confirmed as thoroughly as possible (Kahrilas et al. 2008). The failure of medical treatment has been emphasized in recent guidelines by other authors as well (Stefanidis et al. 2010; Zerbib et al. 2013). The patients with PPI failure are not a uniform group, and there is strong agreement that the reflux-symptom correlation must be established in order to opt for surgery (Fisichella and Patti 2014; Kahrilas et al. 2008; Lundell 2014; Stefanidis et al. 2010; Zerbib et al. 2013).

Surgery has also been recommended for patients with PPI-responsive and objectively verified GERD (Fisichella and Patti 2014), as the surgery has been documented to be

successful in such cases (Anvari et al. 2011; Campos et al. 1999; Galmiche et al. 2011; Morgenthal et al. 2007a). According to the AGA, these patients should be treated with medication, as the medical treatment is considered safer than the operative treatment and the patients may become troubled by some newly-onset symptoms, such as dysphagia, an inability to belch, flatulence, and postoperative intestinal symptoms (Kahrilas et al. 2008).

While most GERD patients can be treated with antisecretory medication, there are some issues concerning conservative treatment even in the case of objectively verified GERD. The response of regurgitation to PPI therapy has been documented to be poor compared to that of heartburn (Kahrilas et al. 2011). Objectively verified GERD is recognized as a chronic condition, and relapses occur unless repeated or continuous medication is used (Hallerback et al. 1994; Isolauro et al. 1997b; Sontag et al. 2006; Vigneri et al. 1995)—yet, in the long term, it was noted that many of the patients became asymptomatic with conservative treatment (Isolauro et al. 1997b). Some patients may not want life-long medication, or compliance with the medical treatment is otherwise poor (Hungin et al. 1999). It has been measured in the US that approximately 30% of heartburn patients experience at least weekly breakthrough symptoms despite the use of PPIs and that 35% are not unequivocally satisfied with the medication (Chey et al. 2010). Albeit extremely rare, there are some proposed complications related to long-term PPI use, such as an increased risk of fractures due to decreased calcium uptake and osteoporosis, clostridium-difficile-associated diarrhea, hypomagnesemia, respiratory infections, chronic kidney disease, dementia, myocardial infection, small intestinal bacterial overgrowth, micronutrient deficiencies, and gastrointestinal malignancies (Cundy and Mackay 2011; Fohl and Regal 2011; Freedberg et al. 2017; Kwok et al. 2012; Moayyedi et al. 2013). Despite the large number of suggested adverse events, the quality of evidence on the subject is low or very low, and the benefits of PPI use for the right indications outweigh the risks (Freedberg et al. 2017).

2.4 The incidence of antireflux surgery

The introduction of LNF increased the number of antireflux procedures performed in Finland (Rantanen et al. 2008; Viljakka et al. 1997). The same development has also been noticed in the US and Sweden (Finks et al. 2006; Sandbu and Sundbom 2010). After the 1990s, the surgery rates have declined closer to the numbers of the pre-laparoscopic era. The fundoplication rate in Finland was 8.8 per 100 000 inhabitants in 1988, 12.8 per 100 000 inhabitants in 1992, and peaked at 27.4 per 100 000 inhabitants in 1999 (Rantanen et al. 2008; Viljakka et al. 1997). The number of laparoscopic operations rose since 1992, with no change in the number of open operations (Rantanen et al. 2008). In the US, the number of antireflux procedures for adults was 6.6 per 100 000 inhabitants in 1994. After 1994, the rates climbed steadily until peaking in 1999 at the level of 15.7 per 100 000 inhabitants. After 1999, the number of operations declined substantially to 11 operations

per 100 000 inhabitants in 2003. Between 1999 and 2003, there was no difference in the proportion of operations managed laparoscopically (69% vs. 68%) (Finks et al. 2006). In Sweden, 720 antireflux operations were performed in 1991. After the introduction of LNF, the numbers peaked in 1997 when the number of antireflux operations was 1035. Since then, the number of antireflux procedures has declined steadily in Sweden, and a return to below the initial level was seen in 2007, when only 531 procedures were performed. The number of open operations has remained stable in Sweden for the last decade, while the number of laparoscopic antireflux procedures has declined from the peak level of 1077 in 1998 to 375 in 2007 (Sandbu and Sundbom 2010). It has been proposed that the rise in the prevalence of antireflux surgery after the introduction of LNF may have stemmed in part from the enthusiasm of the surgeons to offer the surgical management and the patients' more willing acceptance of the less-invasive technique (Rantanen et al. 2008; Sandbu and Sundbom 2010; Viljakka et al. 1997). The decline in the number of antireflux procedures has been speculated to be a result of uncertainty of the overall benefits of the procedure, as well as effective medical treatment (PPIs) as an alternative to surgical treatment and the rapid growth of bariatric surgery (Finks et al. 2006).

2.5 Preoperative work-up

When considering operative treatment, a careful preoperative assessment should be run. The preoperative examinations can be categorized into anatomical (endoscopy, barium esophagram) and functional (pH and impedance monitoring, manometry) studies. Upper gastrointestinal endoscopy can be used to assess the anatomy of the proximal gastrointestinal tract, and erosive reflux disease (ERD) may be revealed. Manometry can exclude motor disturbances of the esophagus, such as achalasia. In the case of non-erosive reflux disease (NERD), the reflux may be discovered by using pH or impedance monitoring (Kahrilas et al. 2008; Stefanidis et al. 2010; Zerbib et al. 2013).

2.5.1 Symptoms

Typical symptoms of reflux syndrome are heartburn and regurgitation. More infrequent symptoms are dysphagia, epigastric pain, and sleep disturbances. In addition, GERD is related to extraesophageal syndromes such as cough, laryngitis, asthma, and dental erosions. The pathology of these atypical symptoms is often multifactorial, while GERD may just be an aggravating cofactor. GERD has also been linked to sinusitis and pulmonary fibrosis (Vakil et al. 2006).

The prevalence of weekly heartburn and/or regurgitation is reported to be 18.1%–27.8% in the US (El-Serag et al. 2004; Jung et al. 2007) and 9.8%–25.9% in Europe (Diaz-Rubio et al. 2004; Isolauri and Laippala 1995; Ronkainen et al. 2005b). Moreover,

32%–66% of people report monthly or annual symptoms (Diaz-Rubio et al. 2004; Isolaari and Laippala 1995; Ronkainen et al. 2005b). The accuracy of diagnosing GERD directly on the basis of heartburn and/or regurgitation is poor. The sensitivity and specificity of symptom-based diagnosis are reported to be 49% and 74%, respectively, when the diagnosis is verified by means of endoscopy, pH monitoring, and a positive response to PPIs (Dent et al. 2010). Moreover, although GERD is a common condition and the majority of the Western populations have at least annual GERD symptoms, there is notable overlap with the symptoms of GERD and irritable bowel syndrome as well as with functional dyspepsia (Gasiorowska et al. 2009; Jung et al. 2007; Lacy et al. 2012). Roughly estimated, 10% of patients suffering from reflux symptoms have functional dyspepsia (Savarino et al. 2008). Achalasia may also cause similar symptoms to GERD (Anderson et al. 2006). A two-week treatment test with PPIs does not significantly enhance the diagnostic accuracy (Bytzer et al. 2012; Dent et al. 2010).

2.5.2 Health-related quality of life assessment in GERD patients

In the Montreal definition and classification of GERD, it was stated that "GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications," and, furthermore, "symptoms related to gastroesophageal reflux become troublesome when they adversely affect an individual's well-being" (Vakil et al. 2006). Hence, by definition, GERD has an impact on the quality of life.

There are basically three different kinds of instruments to measure the quality of life: generic, disease-specific, and symptom severity scales. Health-related quality of life (HRQoL) refers to those aspects of the overall quality of life that affect the physical or mental health. HRQoL can be defined as an individual's or group's perceived physical and mental health over time (Centers for Disease Control and Prevention 2002). In general, the disease-specific instruments and symptom severity scales measure changes in the states of diseases and symptoms without including actual multidimensional questions relating to HRQoL. General HRQoL instruments do facilitate comparisons between different groups, but may not be sensitive enough to detect changes in states of health if the disease's effect on the overall quality of life is only limited (Chassany et al. 2008).

The HRQoL of GERD patients has been documented as being impaired using both generic and disease-specific instruments (Anvari and Allen 2003; Anvari et al. 2011; Djerf et al. 2016; Kamolz et al. 2005; Revicki et al. 1998a; Tosato et al. 2012; Wang et al. 2008). Compared to a general population, the values of pain, emotional well-being, and social function are the most disturbed in GERD patients. There is a correlation between the frequency and severity of GERD symptoms and a patient's functioning and well-being (Revicki et al. 1998a).

The number of instruments for measuring the subjective status of a GERD patient is substantial. Visual analogue scale (VAS) scores provide an easy and straightforward

instrument for grading any symptom (Reading 1989). The Demeester-Johnson reflux scale is commonly used to measure heartburn, regurgitation, and dysphagia in follow-up studies (Demeester et al. 1976). Two popularly used disease-specific symptom scales are the Gastrointestinal Symptom Rating Scale (GSRS) and the Visick score (Revicki et al. 1998b; Visick 1948). Of the general HRQoL instruments, the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and 15D are widely used (Sintonen 2001; Ware et al. 1993). The 15D values of the general Finnish population have been updated regularly (Koskinen et al. 2012).

2.5.3 Endoscopy

In endoscopy, esophagitis, hiatal hernias, strictures, the appearance of the LES, and endoscopic Barrett's esophagus (BE) can be noted and biopsies taken. Endoscopy also has a role in the differential diagnosis of patients with GERD symptoms, as other conditions, such as malignancies, can be ruled out (Fischella and Patti 2014; Stefanidis et al. 2010). The gastroesophageal flap valve can be graded according to the classification presented by Hill (Hill et al. 1996; Figure 3). A positive correlation has been noted between increased grading and esophageal acid exposure as well as hiatal surface area size (Koch et al. 2013).

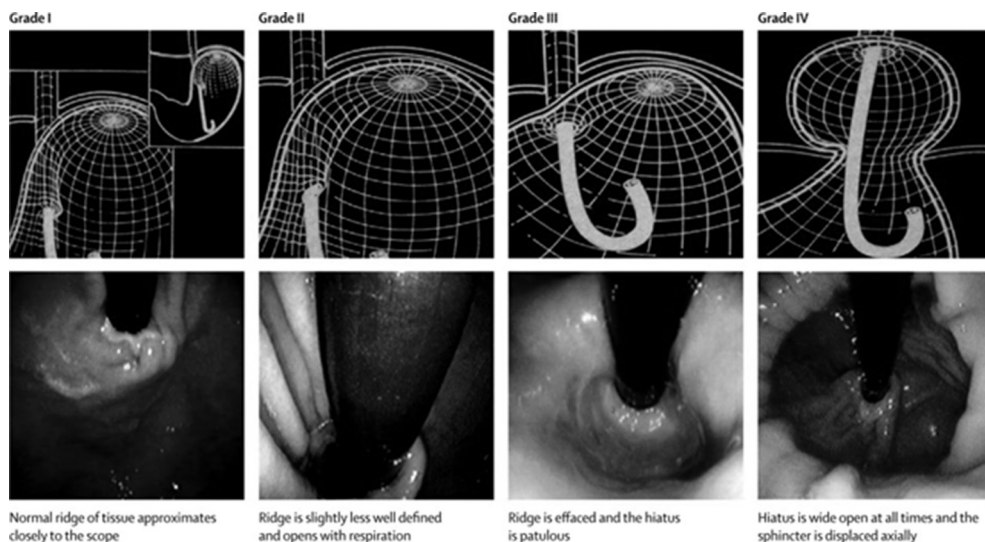


Figure 3. The Hill classification of the gastroesophageal flap valve (Hill et al. 1996). Reprinted with permission.

2.5.3.1 ERD

Approximately 24% of patients with typical reflux symptoms have ERD (Martinez et al. 2003; Ronkainen et al. 2005b). The esophageal mucosal injury is highly specific to GERD, but the sensitivity of endoscopy is low (Fuchs et al. 1987; Stein et al. 1992a). Currently, the Los Angeles (LA) classification of esophagitis is widely used to classify esophagitis (Armstrong et al. 1996; Lundell et al. 1999; Table 1). The Savary-Miller classification was commonly applied previously (Savary and Miller 1977; Table 2). It has been argued that there can be notable inter-observer variability in grading endoscopic findings (Nasseri-Moghaddam et al. 2007).

Table 1. The Los Angeles classification of esophagitis (Lundell et al. 1999)

Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference
Grade D	One (or more) mucosal break which involves at least 75% of the esophageal circumference

Table 2. The Savary-Miller classification of esophagitis (Savary & Miller 1977)

Grade I	One or several non-confluent erosions
Grade II	Several confluent erosions
Grade III	Confluent erosions, surrounding the esophageal circumference
Grade IV	Ulcer(s), strictures, shortening of the esophagus, Barrett's esophagus

A meta-analysis found the mean healing proportion, irrespective of drug dose or treatment duration, in ERD to be $84\% \pm 11\%$ (sd) when treated with PPI therapy (Chiba et al. 1997). Although the patients with ERD have a higher risk of developing strictures than other dyspeptic patients referred to endoscopy (Hvid-Jensen et al. 2011a), the incidence of strictures has been decreasing at the same time as the use of PPIs has increased (Ruigomez et al. 2006). Complications are rare, but the recurrence of the mucosal damage is common when the therapy is interrupted (Sontag et al. 2006).

2.5.3.2 NERD

In NERD, no mucosal breaks can be seen upon endoscopy, while patients suffer from troublesome reflux-associated symptoms (Vakil et al. 2006). The majority of GERD

patients belong to this group, and the challenge is to differentiate between those with true reflux-based symptoms and those with variable other disorders. In 68%–76% of patients reporting typical reflux symptoms, no signs of active inflammation can be detected in endoscopy, and the macroscopical findings are normal in 35%–48% (Martinez et al. 2003; Ronkainen et al. 2005b). A large proportion (42%–63%) of symptomatic patients with negative endoscopy findings have a pathological 24-hour pH monitoring values (Lind et al. 1997; Martinez et al. 2003; Savarino et al. 2008), and 27%–37% of those with normal acid exposure have a positive symptom correlation with acid reflux (acid hypersensitivity) (Kline et al. 2008; Martinez et al. 2003; Savarino et al. 2008). The PPI response of NERD patients has been considered poorer than that of ERD patients, but a recent meta-analysis suggested that the poor response rate has been due to wrong inclusion criteria, as it was found that the pooled estimate of the complete relief of reflux symptoms after four weeks of therapy was 0.72 in ERD patients vs. 0.73 in NERD patients (positive pH test) vs. 0.50 in empirically treated patients vs. 0.49 in patients considered as NERD patients with no pH testing (Weijenborg et al. 2012).

2.5.3.3 Functional heartburn and reflux hypersensitivity

The Rome IV diagnostic criteria for functional heartburn are: 1) burning retrosternal discomfort and pain, 2) no symptom relief despite optimal antisecretory therapy, 3) absence of evidence that gastroesophageal reflux (abnormal acid exposure and symptom reflux association) or eosinophilic esophagitis is the cause of symptoms, and 4) absence of major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis). All of the above must be included, and the criteria must be fulfilled for the last 3 months, with symptom onset having occurred at least 6 months before diagnosis with a frequency of at least twice a week (Aziz et al. 2016). While the diagnostic methods have evolved, the proportion of patients given the diagnosis of functional heartburn has decreased (Bredenoord et al. 2006; Savarino et al. 2008), but, on the other hand, reflux hypersensitivity is included in the Rome IV criteria for functional esophageal disorders, as the pathogenesis of heartburn in reflux hypersensitivity is considered similar as that in functional heartburn (Aziz et al. 2016). Hypersensitivity includes allodynia and hyperalgesia and may consist of peripheral, central, and psychological factors (Zerbib et al. 2012). The morphological changes found in GERD are absent, and the heartburn may arise despite the mucosa being intact in contrast to GERD (Triantos et al. 2015). Also, the cortico-cerebral processing of esophageal signals to stimuli may be different between healthy subjects and patients with GERD and functional heartburn (Zerbib et al. 2012). There is overlap with reflux hypersensitivity and NERD patients, and it has been proposed that, in the future, a histological analysis of esophageal biopsies might further differentiate between the diagnoses (Triantos et al. 2015).

2.5.3.4 Barrett's esophagus

Barrett's esophagus refers to a transformation of the normal stratified squamous epithelium of the distal esophagus to columnar epithelium. GERD associates strongly with esophageal adenocarcinoma (EAC) (Lagergren et al. 1999), and BE is considered a premalignant condition which can develop into adenocarcinoma (Bennett et al. 2015; Fitzgerald et al. 2014).

The reported prevalence of BE has been 0.4%-1.6% in unselected populations (Cameron et al. 1990; Ronkainen et al. 2005a). Of those with and without reflux symptoms, 2.3% and 1.2%, respectively, were diagnosed with BE, while the prevalence in a general population was 1.6% (Ronkainen et al. 2005a). It seems that the prevalence of BE is also significant among those with no GERD history (Cameron et al. 1990; Ronkainen et al. 2005a; Voutilainen et al. 2000), but a more severe form of GERD appears to increase the prevalence of BE, as it was noted in a study concerning patients with reflux symptoms that the overall prevalence of BE was 8.4%, while the prevalence of BE in patients with ERD was 14% (Malfertheiner et al. 2005). The incidence of BE seems to be rising in Western countries (Coleman et al. 2011). BE has been associated with alcohol, smoking, hiatal hernia, esophagitis, male sex, and age (Ronkainen et al. 2005a; Voutilainen et al. 2000).

The definition of the term Barrett's esophagus has varied, and there is no universal consensus on the diagnostic criteria of BE. There is agreement on the requirement of endoscopic identification of columnar mucosa in the esophagus, but the histological features differ in various diagnostic criteria (American Gastroenterological Association et al. 2011a; Bennett et al. 2015; Fitzgerald et al. 2014).

Chronic reflux and inflammation in the esophagus are thought to convert the squamous epithelium to a mucinous columnar epithelium of gastric type. The gastric epithelium can further biochemically intestinalize and start to express cells that are intestine-specific, such as goblet cells (Odze 2011). The dispute over the diagnostic criteria of BE focus mainly on whether intestinal metaplasia (IM) and the presence of goblet cells are required for the diagnosis or not. The former impression that IM with goblet cells carries a much higher risk of malignant progression than other types of metaplasia has been questioned (American Gastroenterological Association et al. 2011a; Bennett et al. 2015; Fitzgerald et al. 2014; Odze 2011). It has been proposed that goblet cells participate in the mucosal defense (Hahn et al. 2009; Odze 2011), and a report has been published suggesting that goblet cells in metaplastic areas have a protective role against cancer progression rather than being indicators for a premalignant condition (Srivastava et al. 2015). However, while the relationship between different stages of metaplasia and the risk for dysplasia remain obscure, the recognition of IM seems to have clinical relevance, as metaplasia, dysplasia, and adenocarcinoma have been reported to develop only in patients with IM (Chandrasoma et al. 2012; Westerhoff et al. 2012), but the wrong biopsy sampling technique would produce a false-negative diagnosis of IM (Chandrasoma et al. 2012). IM appears to be most prevalent in the proximal part of the abnormal epithelium (Chandrasoma et al. 2001), and the

prevalence of IM seems to increase with the length of the metaplastic area (Chandrasoma et al. 2012).

In an observational prospective cohort study, a longer duration and longer length of BE, as well as low-grade dysplasia and esophagitis, were found to be risk factors for BE developing into high-grade dysplasia or EAC (Sikkema et al. 2011). The annual risk of BE developing into EAC has been found to be 0.12%–0.27% (Hvid-Jensen et al. 2011b; Wani et al. 2011), as the relative risk for the patients with BE is 11.3–16.42 times that of the general population (Cook et al. 2007; Hvid-Jensen et al. 2011b).

The need for the surveillance of BE has been questioned (Erichsen et al. 2017), but despite the lack of high-quality evidence concerning the benefits of the endoscopic surveillance of BE, most of the guidelines recommend keeping BE with IM under surveillance (American Gastroenterological Association et al. 2011a; Fitzgerald et al. 2014), while others have suggested no surveillance in case of no dysplasia (Bennett et al. 2015). A surveillance interval of 6–12 months seems to be generally agreed upon in the case of low-grade dysplasia (American Gastroenterological Association et al. 2011b; Bennett et al. 2015; Fitzgerald et al. 2014). The Prague C & M criteria have been developed to measure and grade the BE segment (Sharma et al. 2006).

2.5.3.5 Esophageal adenocarcinoma

BE-related EAC develops through an esophagitis–BE–dysplasia sequence (Bennett et al. 2015). During the last decades, the incidence of EAC has been rising in the Western world (Cook et al. 2009; Lepage et al. 2008). Between 1992 and 2005, the incidence of EAC in the US was 4.8 per 100 000 person years among white men and 1.0 per 100 000 person years among black men. The incidence was 7.65 times higher among white men than white women and 3.64 times higher among black men than black women (Cook et al. 2009). The incidence in the UK and Wales has been reported to be 4.5 per 100 000 among men and 0.9 per 100 000 among women (Lepage et al. 2008). The overall 5-year survival of EAC is low (13%) (Eloubeidi et al. 2003). While EAC has a poor prognosis, it has been found that only 7.4% of patients with IM die of esophageal cancer (Anderson et al. 2003) and, furthermore, only 5.7% of patients die of EAC (Cook et al. 2007). In a Danish study, prophylactic measures against cardiovascular diseases and non-esophageal cancers were seen as potentially more important than the measures against esophageal cancer in BE patients because of the low mortality rates (5.4 per 1000 person years) due to esophageal cancers (Erichsen et al. 2017).

2.5.3.6 Shortened esophagus

Severe GERD may cause a transmural inflammation, leading to a subsequent shortening of the esophagus. Preoperative endoscopy, esophagography, or manometry may give clues of the condition, but the diagnosis may not be revealed until intraoperatively, when excessive mediastinal dissection is needed to mobilize the esophagus. A large paraesophageal hernia is associated with a shortened esophagus (Kunio et al. 2015). Endoscopically verified preoperative findings of either strictures or Barrett's esophagus have been found to be the most accurate test in detecting a short esophagus (sensitivity 80%, positive predictive value 31%; Mittal et al. 2000). A Collis gastroplasty, which can also be performed laparoscopically, or a modification thereof, is recommended to restore the length of the esophagus in order to prevent crural disruption and herniation of the wrap to the mediastinum (Hunter et al. 1999; Kunio et al. 2015; Orringer and Sloan 1978; Terry et al. 2004). The incidence of the need for the lengthening procedure is under debate (Kunio et al. 2015; Migaczewski et al. 2015).

2.5.4 Barium esophagram

In the preoperative work-up of antireflux surgery, the purpose of a barium esophagram is not to diagnose GERD, but rather to clarify the anatomy of the esophagus and stomach. A hiatus hernia, the presence of a Schatzki ring, and the strictures can be visualized (Fisichella and Patti 2014). At present, the barium esophagram is used mainly as an esophageal function test rather than a preoperative test (Katzka 2014). The sensitivity and positive predictive value of a barium esophagram to detect a short esophagus are relatively poor—66% and 37%, respectively (Mittal et al. 2000). Also, the sensitivity and specificity of the test to identify gastroesophageal reflux in patients with positive 24-hour pH monitoring have been discovered to be low, 47% and 70%, respectively (Bello et al. 2013).

2.5.5 Ambulatory 24-hour pH monitoring

Esophageal reflux monitoring is recommended as a part of the preoperative work-up, since especially the lower grades of esophagitis have been found not to correlate with pathological esophageal acid exposure (Bello et al. 2013; Patti et al. 2001). pH monitoring tests provide information on esophageal acid exposure, reflux patterns, and symptom correlation (Han and Peters 2014). A distal esophageal pH of <4 was defined in 1961 by Tuttle et al. as being pathological, since it was observed to cause heartburn (Tuttle et al. 1961). Since then, pH <4 has been verified as a good cut-off limit in detecting reflux (Johnsson et al. 1987). In 1974 Johnson and Demeester established the foundation for 24-hour pH monitoring by defining a six-parameter scoring system and reference values for each parameter. The

parameters and the normal values are: total time pH <4 (<4.2%), upright time pH <4 (<6.3%), supine time pH <4 (<1.2%), no. of reflux episodes (<50), no. of reflux episodes ≥ 5 min (≤ 3.0), and longest episode (<9.2 min). The Demeester total score is calculated as a sum from these by using a specific formula (Han and Peters 2014). In clinical practice, the total time pH of <4 is generally used a variable to detect pathological reflux, for it has been verified to be as good as other single determinants and it is easy to use (Johnsson et al. 1987; Schindlbeck et al. 1987). Along with the traditional 24-hour pH monitoring, there are also 48- and 96-hour devices available with catheters and wireless Bravo-pH capsules (Han and Peters 2014). Normal pH monitoring values have been recorded in 20%–45% of patients with endoscopically confirmed esophagitis (Bello et al. 2013; Patti et al. 2001) and in 37%–58% of patients with reflux symptoms and a negative endoscopy (Lind et al. 1997; Martinez et al. 2003; Savarino et al. 2008). In a study comparing traditional pH monitoring and pH impedance monitoring in a clinical setting, it was found that the number of positive tests was similar in both arms of the patients and that 45%–50% of the patients with negative results were still prescribed PPIs (Pugliese et al. 2016).

2.5.6 Multichannel intraluminal impedance pH monitoring

Impedance refers to electrical resistance in an alternating current circuit. The ionic concentration of the bolus affects the conductivity and impedance, which gives information about the medium and allows impedance monitoring to differentiate between the states of matter (Gyawali et al. 2013). 24-hour multichannel intraluminal impedance pH monitoring (MII-pH) measures the impedance of the esophagus along with distal esophageal acid exposure. It can differentiate between acidic and non-acidic reflux and detect the bolus movements in the esophagus, which helps to identify reflux-symptom correlation (Han and Peters 2014).

The reflux episodes detected by simultaneous impedance and pH monitoring are subcategorized into five groups: 1) acid reflux, 2) superimposed acid reflux, 3) weakly acidic reflux, 4) nonacidic reflux, and 5) pH-only reflux (Sifrim et al. 2004; Table 3).

Table 3. Reflux subcategories (Sifrim et al. 2004)

Acid reflux	pH falls from above to below 4
Superimposed acid reflux	reflux while pH is already <4 from acid reflux
Weakly acidic reflux	pH nadir is ≥ 4 but <7
Nonacid reflux	pH remains ≥ 7 or increases to ≥ 7
pH-only reflux	pH fall from above to below 4, detected by pH probe but not impedance

Normal values for the parameters have been obtained from 60 healthy volunteers (Shay et al. 2004). To further analyze whether the symptoms are reflux-related, a combined

symptom association analysis can be made. The most widely used markers are: symptom index (SI), symptom sensitivity index (SSI), and symptom association probability (SAP). SI is defined as the percentage of symptom episodes that are related to reflux, and $\geq 50\%$ is considered a positive value. SSI means the proportion of symptom-associated reflux episodes out of the total number of reflux episodes ($\geq 10\%$ positive). SAP is a parameter that indicates the probability of the symptoms being related to reflux episodes. The statistical relationship between symptoms and reflux episodes using Fisher's exact test is calculated ($\geq 95\%$ positive) (Bredenoord et al. 2005).

In clinical practice, the MII-pH- monitoring can be used in diagnosing GERD in patients with atypical symptoms or PPI-refractory disease (Han and Peters 2014), or in NERD patients with negative 24-hour pH monitoring (Bredenoord et al. 2006; Kline et al. 2008; Savarino et al. 2008). Good outcomes after LNF have been described in patients with negative acid exposure but positive MII-pH results (del Genio et al. 2008).

2.5.7 Manometry

Manometry systems recognize the timing and the amplitude of pressure changes in the esophagus by using an intraluminal catheter. With esophageal manometry, one can assess the motility of the esophageal body and the function and location of the esophageal sphincters (Gyawali et al. 2013). The localization of LES aids in guiding the pH or impedance monitoring catheter into place. Along with motor disturbances, an important objective of manometry is to diagnose achalasia, which can cause similar symptoms to GERD (Anderson et al. 2006). It has been noted that the motor function of the esophagus deteriorates and the prevalence of a mechanically defective LES increases with increasing mucosal damage (Kahrilas et al. 1986; Stein et al. 1990; Stein et al. 1992b). Based on the values obtained from 50 healthy individuals, the LES can be considered incompetent if the mean resting pressure is below 6 mmHg and the total and intra-abdominal lengths of the LES are inadequate (Zaninotto et al. 1988). In the 1990s, high-resolution manometry, which provides a more detailed analysis of the esophageal pressure profile, became available (Gyawali et al. 2013). The Chicago classification provides a hierarchical analysis of high resolution manometry studies and criteria to classify different motility disorders (Bredenoord et al. 2012). Currently, high-resolution manometry is considered superior to conventional manometry as far as diagnostic accuracy and the ease of interpretation are concerned (de Bortoli et al. 2016; Soudagar et al. 2012).

2.6 Postoperative follow-up

2.6.1 Subjective outcome

2.6.1.1 Postoperative symptom relief

Usually, typical symptoms of GERD are relieved markedly after LNF, whereas dysphagia increases. While LNF provides extremely efficient control of heartburn and regurgitation in the short term, the results have been noted to deteriorate to some extent in the long term (Kellokumpu et al. 2013; Morgenthal et al. 2007b). After 10–11 years' follow-up, 57%–65.7% and 70.9%–78.9% of patients report complete resolution of heartburn and regurgitation, respectively. Moderate to severe heartburn and regurgitation are reported by 5.1%–24.2% and 1.3%–7.8%, respectively (Broeders et al. 2009b; Kellokumpu et al. 2013; Morgenthal et al. 2007b).

2.6.1.2 Patient satisfaction

After LNF, 73.1%–92.7% of the patients are reported to be satisfied with the results, while 2.1%–15% are dissatisfied (Mehta et al. 2006; Morgenthal et al. 2007b; Salminen et al. 2012; Tucker et al. 2005; Vakil et al. 2003). In retrospect, 77.1%–93.3% of the patients would choose surgery again (Broeders et al. 2009b; Morgenthal et al. 2007b; Salminen et al. 2012; Shaw et al. 2010).

2.6.1.3 Improvements in health-related quality of life

The HRQoL is demonstrated to improve markedly after LNF, when measured using both disease-specific and generic quality of life instruments (Anvari and Allen 2003; Broeders et al. 2009b; Djerf et al. 2016; Galmiche et al. 2011; Kamolz et al. 2005; Tosato et al. 2012; Wang et al. 2008). The results concerning HRQoL have also been reported to endure in the long term (Broeders et al. 2009b; Djerf et al. 2016), and when compared to the results of healthy individuals or a general population, the outcome has been similar or close (Anvari and Allen 2003; Anvari et al. 2011; Djerf et al. 2016; Kamolz et al. 2005; Kellokumpu et al. 2013; Koetje et al. 2016; Tosato et al. 2012). The failure of the treatment or dissatisfaction with the treatment is associated with lower HRQoL scores (Kellokumpu et al. 2013; Koetje et al. 2016).

2.6.1.4 Treatment-related side effects

2.6.1.4.1 *Dysphagia*

Dysphagia is very common shortly after the operation, possibly due to inflammation and edema. In most cases, dysphagia is resolved significantly after the next few months and continues to diminish over the following years (Broeders et al. 2011b; Luostarinen et al. 2001; Negre 1983). In general, after 10–15 years' follow-up, 7.8%–12.0% of patients report moderate to severe dysphagia, while 46.2%–70.5% have no dysphagia (Broeders et al. 2009b; Kellokumpu et al. 2013; Morgenthal et al. 2007b; Salminen et al. 2012). Only a minority of the patients will require interventions for persistent dysphagia. The problems behind excessive persistent dysphagia may stem from a paraesophageal hernia, herniation of both the wrap and the GEJ above the diaphragm, a slipped fundoplication, a tight esophageal hiatus, and a too tight or too long wrap (Horgan et al. 1999; Lamb et al. 2009; Stein et al. 1996). Other proposed causes include a peptic esophageal stricture, ineffective esophageal motility, recurrent reflux esophagitis, achalasia missed preoperatively, and achalasia developed postoperatively (Spechler 2004; Stein et al. 1996). Reoperation rates of 5.1%–7.7% (Broeders et al. 2011b; Broeders et al. 2009b; Yang et al. 2012) and dilatation rates of 4.0%–14% (Broeders et al. 2011b; Morgenthal et al. 2007b; Yang et al. 2012) for dysphagia after LNF have been reported. After dilatation, 68.6% of the patients are reported to have a good outcome, while 62.7% of those requiring revisional surgery because of dysphagia were satisfied with the late outcome (Yang et al. 2012). It has been proposed that patients with a clear anatomic defect, such as a slipped wrap or a paraesophageal herniation, respond poorly to dilatation (Horgan et al. 1999).

2.6.1.4.2 *Gas-bloat syndrome and flatulence*

The usual side effects of fundoplication are related to the reduced ability to vent gas from the stomach into the esophagus after the operation. This group of symptoms is also referred to as gas-bloat syndrome. Patients report bloating, abdominal distention, an inability to belch, an inability to vomit, early satiety, nausea, upper abdominal pain, and flatulence (Spechler 2004). In a Swedish study, gas-bloat symptoms and/or flatulence was most frequently identified as the most bothersome postoperative symptom (46.8%) (Sandbu et al. 2002). In the long term, decreased belching (61.2%), increased flatulence (91.4%), increased bloating (71.9%), and the inability to vomit (30.9%) have been reported (Kellokumpu et al. 2013), while only 20.9% of patients reported no or mild bloating and flatulence and 45.8% had difficult to severe bloating and flatulence (Salminen et al. 2012). The patients with an intact fundoplication wrap have been reported to experience more bloating and flatulence than those with a defective plication (Salminen et al. 2012).

Many of the symptoms related to gas-bloat syndrome are associated with delayed gastric emptying, a condition which has been reported to be a rather prevalent condition in

GERD patients (0%–51%), although the delayed emptying has not been proved to promote reflux (Penagini and Bravi 2010). While antireflux surgery has been noted to improve and normalize gastric emptying in the majority of patients (Lindeboom et al. 2004; Viljakka et al. 1999), those patients who had suffered from delayed gastric emptying preoperatively were also reported to have more gas-bloating, abdominal pain, and nausea postoperatively, even if the symptoms had improved after the operation (Khajanchee et al. 2009).

The division of the SGVs has been associated with increased bloating (Engstrom et al. 2011), and transient LES relaxations, caused by gastric distension with air, have been manometrically documented to occur more often in patients with intact SGVs than in patients with a division of all SGVs, suggesting a reduced air-venting ability after gastric mobilization (Engstrom et al. 2004). A study after floppy LNF found that the belching pattern changed from gastric belches, which vent air from the stomach, to supragastric belches with no air-venting and thus increased the gas-bloat symptoms and flatulence. In addition, in a third of the patients, there was a positive relationship between postoperative symptoms and gastric or supragastric belches (Broeders et al. 2011a).

Most patients with postoperative gas-bloat symptoms are treated conservatively, but the patients with severe symptoms may require an evaluation for small bowel obstruction caused by adhesions or delayed gastric emptying in the case of inadvertent vagotomy (Spechler 2004).

2.6.1.4.3 *Diarrhea*

After laparoscopic antireflux surgery, 12.3%–35.5% of the patients report diarrhea (Bammer et al. 2001; Klaus et al. 2003; Kornmo and Ruud 2008). In a study by Klaus et al., new-onset diarrhea developed in 18% of the patients. In their study, 35% of the patients had bowel symptoms before surgery (Klaus et al. 2003). Ranson et al. reported that 58% of the patients had diarrhea at either the preoperative or postoperative evaluation—in 60% of the cases, the diarrhea improved and in 20% worsened after LNF (Ranson et al. 2007). Overlap between irritable bowel syndrome and GERD may explain the postoperative diarrhea to some extent (Gasiorowska et al. 2009). Fundoplication is noted to accelerate gastric emptying (Lindeboom et al. 2004; Viljakka et al. 1999), which is proposed to contribute to a more swift intestine transit time and diarrhea (Klaus et al. 2003). In addition, the patients with preoperatively delayed gastric emptying who underwent LNF and pyroloplasty were reported to have a high incidence of diarrhea postoperatively (Khajanchee et al. 2009). An inadvertent vagus nerve injury may lead to severe diarrhea (Ukleja et al. 2002), while the 10% of patients found to have signs of vagus nerve dysfunction after partial fundoplication did not differ from the other patients as regards GERD symptoms, 24-hour pH studies, or gastric emptying (Lindeboom et al. 2004). In general, most of the follow-up studies neglect a systematic approach in dealing with diarrhea as a postoperative symptom.

2.6.2 Failure after fundoplication

The definition of failure after fundoplication has proven difficult since there is discrepancy between patient-perceived symptoms and the results of objective investigation methods. It has been noted that only 29.3%–39% of patients with persistent symptoms after laparoscopic total or partial fundoplication have an abnormal 24-hour pH study (Galvani et al. 2003; Khajanchee et al. 2002), while 11.9% of asymptomatic patients have pathological scores (Khajanchee et al. 2002). Postoperative regurgitation predicts abnormal pH monitoring, whereas heartburn, dysphagia, and chest pain are equally prevalent in patients with abnormal and normal pH studies (Galvani et al. 2003). In a study by Broeders et al., no acid or weakly acidic reflux was found behind persistent reflux symptoms after LNF. Instead, in a third of symptomatic patients, a positive correlation was found between reflux symptoms and gastric belches or supragastric belches. It was noted that LNF decreases liquid-containing reflux to a larger extent than gas reflux (Broeders et al. 2011a). In Salminen's study, no statistically significant symptomatic difference was found between the groups of open and laparoscopic Nissen fundoplications, although 46.4% of the wraps were endoscopically determined to be partially or totally disrupted in the open group vs. the 11.1% in the laparoscopic group; however, the defective wraps were associated with heartburn and regurgitation, more common use of PPIs, and a more negative evaluation of the result of surgery (Salminen et al. 2012).

2.6.2.1 Postoperative use of antisecretory medication

In a Danish population-based follow-up study consisting of patients who underwent antireflux surgery during 1996–2010, the 5-, 10-, and 15-year cumulative risks of redeeming an index PPI prescription were 57.5%, 72.4%, and 82.6%, respectively. The 5-, 10-, and 15-year risks of long-term PPI use were 29.4%, 41.1%, and 56.6%, respectively (Lodrup et al. 2014). In the studies concerning LNF with 10–15-year follow-up periods, 26.6%–46.5% of patients have used PPIs, while the study by Morgenthal also included H2As (30% overall use) (Broeders et al. 2009b; Morgenthal et al. 2007b; Salminen et al. 2012).

Although a large number of patients use antisecretory medication postoperatively, objectively verified refractory reflux has been documented only for a minority of the patients. Only 24%–32% of patients taking acid-reducing medications have an abnormal pH monitoring (Galvani et al. 2003; Lord et al. 2002). Broeders et al. studied 20 patients dependent on daily PPIs 10 years after LNF or open Nissen fundoplication (ONF) using 24-hour MII-pH and found no reflux in 65% of the patients; six patients had acid reflux, and one patient had physiological acid exposure with a positive symptom-reflux correlation. No association between manometric studies and acid exposure or symptomatic outcome was found, with the exception of high-resolution manometry according to which 40% of the patients had LES dysrelaxation, which was associated with retrosternal pain and

may have caused the resumption of PPI use (Broeders et al. 2009b). Salminen et al. found an objective endoscopic explanation for daily PPI use in only half of the patients taking medication after fundoplication (Salminen et al. 2012).

2.6.2.2 Complications, conversions, and reoperations

The rate of serious complications in a Finnish national-based analysis was 0.7% after LNF (Rantanen et al. 2008), while in a Danish nationwide study it was 1.3% after primary operations (LNF + ONF) and 1.6% after reoperations (Funch-Jensen et al. 2008). The serious complications in the Finnish study (LNF+ONF) were esophageal perforation 0.2%, gastric perforation 0.2%, dysphagia 0.1%, and, more seldom, in descending order: a complicated paraesophageal hernia, intestinal complications, deep surgical infections, intra-abdominal bleeding, and pulmonary embolism (Rantanen et al. 2008).

The 30-day mortality rates were 0.04% (LNF) and 0.46% (LNF+ONF) in the Finnish and Danish data, respectively. The mortality was most often caused by an esophageal or gastric perforation (Funch-Jensen et al. 2008; Rantanen et al. 2008). In the Danish data, one patient died because of a paraesophageal herniation, and the mortality was higher due to medical complications (cardiopulmonary n=5, stroke n=1) than to operative complications (Funch-Jensen et al. 2008).

Conversion rates of 6.1%–7.6% have been reported after LNF (Broeders et al. 2009b; Funch-Jensen et al. 2008; Salminen et al. 2012).

Reoperation rates of 5.5%–15.2% have been reported after LNF (Broeders et al. 2009b; Morgenthal et al. 2007b; Salminen et al. 2012; Shaw et al. 2010), while the five- and ten-year cumulative reoperation rates in the Californian database were 5.2% and 6.9%, respectively (Zhou et al. 2015). The reoperation rate at Tampere University Hospital during the ONF era was 3% (Luostarinen et al. 1993a). The Danish nationwide reoperation rate, including ONF, was 5.0% (Funch-Jensen et al. 2008). The reoperation rate is the highest during the first year, after which it steadily declines up until four years postoperatively (Funch-Jensen et al. 2008; Zhou et al. 2015).

2.6.2.3 The incidences of recurrent esophagitis, defective fundic wraps, and esophageal acid exposure after the operation

The reported incidences of recurrent esophagitis have varied between 0%–29% after LNF and ONF (Broeders et al. 2010a; Broeders et al. 2010b; Djerf et al. 2016; Galmiche et al. 2011; Luostarinen 1993; Luostarinen et al. 1993b; Rantanen et al. 1999; Salminen et al. 2007), while the proportion of defective fundic wraps has been 0%–46% (Djerf et al. 2016; Luostarinen 1993; Luostarinen et al. 1993b; Rantanen et al. 1999; Salminen et al. 2012; Salminen et al. 2007). The incidence of defective wraps has been lower after LNF

(0%–13%) than ONF (23%–46%), while there are only two series with an endoscopic assessment of the state of the wrap after LNF, and the study by Djerf et al. only included 13 patients (Djerf et al. 2016; Salminen et al. 2012; Salminen et al. 2007). pH monitoring has revealed pathological acid exposure in 0%–22.7% of patients after LNF or ONF (Broeders et al. 2010a; Djerf et al. 2016; Luostarinen 1993), and the total acid exposure time in the patient groups has varied between 0.7% and 2.9% after LNF (Anvari et al. 2011; Broeders et al. 2010b; Broeders et al. 2013; Galmiche et al. 2011).

2.6.2.4 Failure patterns documented in reoperations

In the studies dealing with failure patterns observed in reoperations after antireflux procedures, the main symptoms of the patients referred for an evaluation of revisional surgery are heartburn and regurgitation (29%–44.7%), dysphagia (31%–32.3%), and both dysphagia and reflux symptoms (15.2%–27%). Other symptoms, such as gas bloating, diarrhea, abdominal pain, and “gastric denervation symptoms” were reported to be the main symptoms in 7.6%–13% of the cases (Horgan et al. 1999; Stein et al. 1996). The typical reflux symptoms and postoperative use of PPIs are more often found in patients with a defective fundoplication, while bloating and flatulence are more common with patients with an intact wrap (Salminen et al. 2012). Most of the technical failures are detected during the first few years after the primary operation. Hunter et al. reported that 90% of the reoperations are performed during the first two years, while Lamb et al. reported that 64.2% are performed during the first three years, whereas the median interval between the operations was 26 months (Funch-Jensen et al. 2008; Hunter et al. 1999; Lamb et al. 2009; Zhou et al. 2015).

Horgan et al. classified technical failures in three categories based on endoscopic, radiologic, and operative findings (Figure 4). In Type I failures, the GEJ is above the diaphragm. Type I failures are further divided into type IA, in which both the GEJ and the wrap are above the diaphragm, and to type IB in which only the GEJ is above the diaphragm. In type II failures, a portion of the wrap has migrated up through the crura, thus forming a paraesophageal hernia. In type III failures, the wrap is malformed because the fundoplication is made from the body of the stomach instead of the fundus (Horgan et al. 1999). Other types of failures noted include: a disruption of the wrap, a too long or a too tight wrap, a twisted fundoplication, esophageal motor disorders, and gastric denervation (Hunter et al. 1999; Stein et al. 1996).

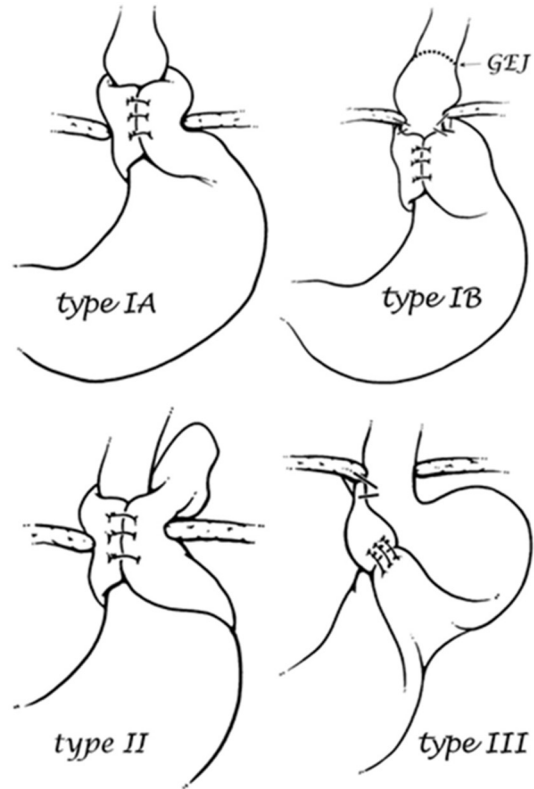


Figure 4. Classification of fundoplication failures (Horgan et al. 1999). Reprinted with permission.

After the introduction of the laparoscopic technique, acute paraesophageal herniation was recognized to become more common, and posterior hiataloplasty was recommended (Watson et al. 1995). In the studies by Lamb et al. and Hunter et al. concerning reoperations after laparoscopic funduplications, it was noted that most of the causes of failure were related to an unsuccessful hiatal closure and/or to the subsequent herniation of the wrap or parts thereof through the hiatus (Hunter et al. 1999; Lamb et al. 2009; Table 4). Horgan et al. classified failures after various different types of antireflux procedures (both laparoscopic and open techniques) as follows: type IA 41.9%, type IB 16.1%, type II 16.1%, and type III 6.5% (Horgan et al. 1999). Stein et al. reported failures in patients referred for a reoperation evaluation after various types of open antireflux procedures as follows: disruption of the wrap 45.7%, slipped wrap 22.9%, too tight or too long wrap or a too tight hiatal closure

Table 4. The causes of failure after laparoscopic funduplications (Hunter et al. 1999; Lamb et al. 2009)

hiatal disruption / herniation	25.7–50.7%
too tight hiatus	23.9%
twisted fundoplication	19.7%
slipped fundoplication	3.7–18.3%
achalasia	5.6%
too tight / too long wrap	3.7–4.2%
disruption of the wrap	1.4%

10.5%, esophageal motor disorder 9.5%, herniation 5.7%, and gastric denervation 5.7% (Stein et al. 1996). In the study conducted at Tampere University Hospital after ONF, the failures were due to slipping (66%) and disruption (33%) (Luostarinen et al. 1993a).

A paraesophageal hernia, a herniation of both the wrap and the GEJ above the diaphragm, a slipped fundoplication, a tight esophageal hiatus, and a too tight or too long wrap are associated with persistent dysphagia (Horgan et al. 1999; Lamb et al. 2009; Stein et al. 1996). No response to dilatations was reported in the case of a slipped wrap or paraesophageal herniation (Horgan et al. 1999). Recurrent reflux symptoms are found with a disruption of the wrap, herniation of the wrap, slipped wrap, and a paraesophageal hernia (Horgan et al. 1999; Lamb et al. 2009; Stein et al. 1996). Roughly half of the patients (48%) with recurrent reflux symptoms are reportedly treated conservatively, while a reoperation is more often required in patients with dysphagia or reflux symptoms and dysphagia (86.3%) (Stein et al. 1996). Patients who had a reoperation because of dysphagia have been noted to have a higher incidence of poorly controlled heartburn and troublesome dysphagia as well as a lower satisfaction score than those operated on because of recurrent reflux or a paraesophageal hernia (Lamb et al. 2009). A wrap disruption is more common after open than laparoscopic fundoplication (Hunter et al. 1999; Salminen et al. 2012).

To prevent wrap herniation, Horgan et al. recommended fixing the wrap to the esophagus and to the undersurface of the crura (Horgan et al. 1999), while Hunter et al. stated that the fixation to the undersurface of diaphragm did not seem to prevent the complication. Hunter et al. proposed that the scarce formation of adhesions on the posterior side of the esophagus after laparoscopic fundoplication and a short esophagus may predispose to the herniation of the wrap and suggested thorough esophageal mobilization and firm crural closure as a means of prevention as well as Collis gastroplasty in the case of advanced esophageal disease when a fundoplication herniation develops without an identifiable event causing hiatal disruption (Hunter et al. 1999). A paraesophageal hernia is proposed to be the result of a redundant fundoplication and defective diaphragmatic closure (Horgan et al. 1999). The study from Tampere supports this, as 90% of the wrap herniations occurred when the fundus was mobilized and hiatoplasty was not performed (Luostarinen and Isolauri 1999a). The factors leading to wrap disruption have been suggested to include insufficient fundic mobilization, a failure to fix the wrap to the cardia, and the use of absorbable suture material (Stein et al. 1996).

2.6.3 Methods to diagnose failure in clinical setting

Although there are many instruments available for the subjective evaluation of a GERD patient, the data assessing the suitability of these instruments as outcome measures is scarce. In a review by Vakil et al., it was noted there were no patient-reported outcome instruments meeting the requirements of the US Food and Drug Administration and the European Medicines Agency. The US Food and Drug Administration and the European

Medicines Agency emphasize the importance of taking the patients' experiences into account in symptomatic diseases in order to enhance the content validity (Vakil et al. 2013). Two studies comparing the disease-specific Gastroesophageal Reflux Disease-Health-Related Quality of Life (GERD-HRQL) instrument and SF-36 found the disease-specific instrument to correlate better with patient satisfaction and heartburn. GERD-HRQL is a symptom-rating questionnaire in which six out of ten questions concern heartburn, with no questions dealing with the possible side effects of treatments (Koetje et al. 2016; Velanovich 1998). The GERD-HRQL score and pH test result have been found to not correlate in patients with achalasia after Heller myotomy and Dor fundoplication (Gholoum et al. 2006). The Visick score has been noted to correlate with heartburn and quality of life tests, but not with pH monitoring (Rijnhart-De Jong et al. 2008). There is no instrument for the subjective evaluation of a patient to replace a systematic interview consisting of postoperative symptoms, patient satisfaction, and the need for antisecretory medication.

In upper gastrointestinal endoscopy, the esophageal and gastric mucosa can be evaluated and the status of the fundoplication seen. The failures related to the wrap create distinct appearances, and endoscopic classifications have been proposed to categorize postoperative states (Jobe et al. 2004; Koch et al. 2013). In 75%–90% of patients with an endoscopically defective wrap and in 2.6%–16% of patients with an intact wrap, pathological acid reflux has been measured after fundoplication (Braghetto et al. 2012; Lord et al. 2002; O'Hanrahan et al. 1990)

A barium esophagram gives information about the anatomy and the relationship of the GEJ with the hiatus, and it also facilitates the assessment of esophageal emptying (Horgan et al. 1999; Spechler 2004). Radionuclide transit has also been used to study esophageal clearance after fundoplication (Luostarinen et al. 2001). Barium contrast has been found inferior to endoscopy in detecting esophagitis as well as slipping and disruption of the wrap, while a too tight wrap was detected more often (Jailwala et al. 2001). Of the patients with radiologically defective wraps, 90.9% have been demonstrated to suffer from pathological acid reflux, while 9.5% of the patients with intact wraps had pathological acid exposure (Braghetto et al. 2012).

Computer tomography (CT) can be used to obtain information about the condition of the fundoplication wrap. Typical features of contrast-enhanced CT scans depicting normal anatomy as well as common failures after Nissen fundoplication have been published (Carbo et al. 2014; Pavone et al. 1997).

Magnetic resonance fluoroscopy is a dynamic non-invasive method to evaluate the anatomy and function of the GEJ. A study including 21 patients with recurrent reflux symptoms and 8 asymptomatic patients after LNF demonstrated that MR fluoroscopy could detect a slipped wrap in 67%, a wrap disruption in 100%, too tight crural sutures or too tight wrap in 100%, and recurrent reflux in 50% of the cases. Magnetic resonance fluoroscopy could determine the position of the wrap in 93% of the patients. The results

were compared to the operative findings or to endoscopy, manometry, pH monitoring, and barium swallow results. Although the study was not designed to compare different diagnostic methods, magnetic resonance fluoroscopy was found more accurate than endoscopy or barium swallow in detecting failures among the wraps (Kulinna-Cosentini et al. 2014).

Postoperative pathological acid reflux and symptom correlation can be detected with 24-hour pH monitoring (Spechler 2004). MII-pH can be used to diagnose acid, weakly acidic, and alkaline reflux and to examine the composition of the refluxate, as well as to evaluate symptoms caused by belching (Broeders et al. 2011a). MII-pH can be performed on patients on and off PPI therapy (Weigt et al. 2007).

Esophageal manometry can reveal esophageal motor dysfunction, such as achalasia (Spechler 2004). In postoperative high-resolution manometry, in addition to evaluating esophageal peristalsis and the pressure profile of the LES, a hiatal hernia can be detected as a dual high-pressure zone. High-resolution manometry has been noted to be less sensitive than endoscopy and/or a radiologic examination to diagnose hiatal hernia (Tatum et al. 2010).

2.7 Long-term results of Nissen fundoplication

The literature review of this thesis focuses on the long-term results of LNF. The results of ONF are reviewed in order to complete the general view or when the corresponding results after LNF are lacking.

2.7.1 Technical factors influencing the outcome

Some modifications of the original operative technique of Rudolph Nissen have been proposed to prevent failures and unwanted side effects. The use of laparoscopy has led to further developments in the operation.

2.7.1.1 HiatoPlasty

Reducing the hiatal opening is considered an essential part of a successful laparoscopic fundoplication, since hiatal disruption detected in reoperations is reported as being the most common reason for failure (Horgan et al. 1999; Hunter et al. 1999; Lamb et al. 2009; Watson et al. 1995). There are no randomized studies evaluating laparoscopic fundoplications with or without hiatal closure. In a prospective randomized controlled trial (RCT) comparing LNFs with posterior hiatoPlasty and LNFs with posterior hiatoPlasty with an onlay of polytetrafluoroethylene mesh in treating large (≥ 8 cm in diameter) hiatal hernias,

the recurrence rate in the barium esophagram was higher (22% vs. 0%) in the group with no mesh. No mesh-related complications were reported (Frantzides et al. 2002). Another RCT compared LNFs with posterior sutured hiatoplasty and LNFs with posterior sutured hiatoplasty with an onlay of polypropylene mesh. The rates of intrathoracic wrap migration were 26% in the first-mentioned group vs. 8% in the latter. More postoperative dysphagia was reported in the group with the mesh, while after one year there was no difference in the dysphagia rate. No mesh-related complications were reported (Grandrath et al. 2005). It has been noted that polypropylene forms adhesions to adjacent organs and, in order to avoid issues relating to this, the use of polytetrafluoroethylene has been proposed with its decreased adhesion formation (Frantzides et al. 2002). Also, biological prostheses have been used for expected safety reasons. A third RCT compared suture closure of the hiatus to a hiatoplasty with an onlay of mesh made from porcine small intestinal submucosa. After six months, the recurrence rates were 24% and 9%, respectively, as diagnosed using a barium esophagram. No mesh-related complications were detected (Oelschlager et al. 2006). It has been suggested that the complications related to meshes are probably more common than previously reported, and the complications have been described with all types of meshes with no apparent relationship between the type and configuration and the complication. The detected complications include intraluminal mesh erosion, esophageal stenosis, and dense fibrosis. The literature reports complication rates from 1.3% to 20%, but the lack of long-term follow-ups may underestimate the rate (Soricelli et al. 2009; Stadlhuber et al. 2009; Trus et al. 1997). Even when using meshes, it has been noted that the larger the hiatal surface area, the more common the recurrence of a hiatal hernia (Koch et al. 2011).

2.7.1.2 Esophageal bougie

In 1986 it was reported that enlarging caliber of the esophageal bougie during fundoplication decreased the incidence of temporary dysphagia (DeMeester et al. 1986). In the laparoscopic era, a bougie has been widely used, even though there is little scientific evidence on the subject. The only reported RCT compared the use of a 56 Fr bougie (n=81) with no calibration (n=90). There was no difference in the dysphagia rates one month postoperatively, but after a follow-up of 11 months, dysphagia was present in 17% of the bougie group and in 31% of the group without a bougie (p=0.047). One patient had an esophageal mucosal laceration from the use of a bougie (Patterson et al. 2000). A retrospective analysis of 82 consecutive patients who underwent LNF revealed no difference in postoperative dysphagia at any point during a one-year follow-up irrespective of whether a 56 Fr bougie was used (the first 40 patients) or not (the latter 42 patients) (Somasekar et al. 2010). A small study prospectively followed 28 consecutive patients who underwent paraesophageal hernia repair and dorsal 270° fundoplication laparoscopically. A 56 Fr bougie was used in the first 14 patients. No difference was found between the groups' dysphagia scores preoperatively or six months postoperatively (Ng et al. 2009). In

a laparoscopic foregut surgery, a 0.8% esophageal or gastric perforation rate during the insertion of a bougie or a nasogastric tube has been reported in a retrospective review at five institutions (n=1620) (Lowham et al. 1996).

2.7.1.3 Division of the short gastric vessels and Nissen-Rossetti

There are two RCTs reporting the long-term results of the division versus non-division of the SGVs ten years after the operation. In both studies, the fundoplication was made using the anterior aspect of the fundus (i.e. Nissen-Rossetti) in the non-division group (Mardani et al. 2009; Yang et al. 2008). A meta-analysis combining these two studies has also been published (Engstrom et al. 2011). No differences were found as regards the reflux symptoms or dysphagia between the two groups, while bloating was significantly more common if the SGVs were divided (72% vs. 48%). In the meta-analysis, it is stated that the SGVs should not be divided and the long-term outcome following LNF is actually worse if the vessels are divided (Engstrom et al. 2011). A similar result with good outcomes for both of the groups, with the exception of increased bloating (19% vs. 38%), has been reported in an RCT from a different series with a one-year follow-up (Chrysos et al. 2001). In an RCT with four years' follow-up, no difference was observed in bloating (Ielpo et al. 2011). The operating time is longer when the SGVs are divided (60–90 min vs. 100–115min) (Chrysos et al. 2001; Ielpo et al. 2011).

2.7.1.4 Fibrin glue

There are three experimental animal studies reporting the use of fibrin glue to enhance the scar formation between the serosal folds of the fundoplication wrap and the esophagus. Lima et al. found all the wraps macroscopically intact two months later in ten suckling pigs (Lima et al. 1997). Isolauri et al. found macroscopical and microscopical scar formation to occur only when fibrin glue was used, while there was no scar formation in the groups with sutures alone, sutures with Teflon pledgets, or sutures with mesh. Immunohistochemistry and histological examinations confirmed the findings (Isolauri et al. 1997a). Doi et al. found in pigs that rubbing sandpaper against the surfaces of the right and left gastric fundi makes the wrap and the crura promote more scar formation macroscopically and microscopically than fibrin glue or sutures alone three months after the operation (Doi et al. 2008).

2.7.1.5 Learning curve

The operating time, complication rate, conversion rate, and reoperation rate have been found to be higher during a surgeon's 20 first LNFs and the highest during the first five. After having operated beyond 20 LNFs, the surgeons reached a plateau with little

further improvement (Watson et al. 1996). In addition to the aforementioned parameters, dysphagia, dilatations, and hospitalization were reduced when the surgeon had experience of more than 30 LNFs compared to an experience of more than five. On the other hand, at five years, there was no difference in the results of objective testing among the patients operated by surgeons with different levels of experience (Broeders et al. 2011c). The institutional plateau has been proposed to be reached after 50 operations (Watson et al. 1996). Also, after ONFs, the results have been noted to improve in relation to the surgeon's experience as regards reoperations, the number of defective wraps, and the symptomatic status of the patients (Luostarinen and Isolaari 1999b).

2.7.2 Long-term results of open Nissen fundoplication

More than 60 years after the introduction of Nissen fundoplication, there are long-term follow-up studies reporting results with 9.8–20 years' follow-up after ONF (Broeders et al. 2009b; Lundell et al. 2009; Luostarinen et al. 1993b; Mardani et al. 2011; Salminen et al. 2012). The long-term symptomatic outcome after LNF and ONF has been proven to be similar (Broeders et al. 2009b; Salminen et al. 2012). The rates of patients having no heartburn have been 60.0–64.7, whereas the corresponding figures for regurgitation have been 64.7–80.6 in long-term follow-up studies. The percentages of moderate to severe heartburn and regurgitation have been 9.0–24.0 and 9.0–17.6, respectively (Broeders et al. 2009b; Luostarinen et al. 1993b; Mardani et al. 2011). Lundell et al. reported approximately 9% of patients having heartburn and 11% of patients having regurgitation, with no further classification of the symptoms (Lundell et al. 2009). In Salminen's study, heartburn and regurgitation were dealt with as one entity, and 42.1% of the patients were noted not to have heartburn and regurgitation while 23.7% suffered from moderate to severe heartburn and regurgitation (Salminen et al. 2012). The number of patients reporting moderate to severe dysphagia has been 10.5%–40% (Broeders et al. 2009b; Luostarinen et al. 1993b; Salminen et al. 2012), while bloating and flatulence have been reported variedly. Mardani et al. reported approximately 47% and 35% of patients suffering from moderate to severe flatulence and bloating, respectively (Mardani et al. 2011). Salminen et al. reported 79.1% of patients having moderate to severe flatulence and/or bloating (Salminen et al. 2012), whereas Luostarinen et al. found that 48% of the patients had increased flatulence and/or bloating (Luostarinen et al. 1993b). Lundell et al. reported that approximately 61% of the patients expressed complaints of flatulence (Lundell et al. 2009). Patients are more satisfied with the surgical results after LNF than ONF, and the risks of surgical intervention and incisional hernias are higher after ONF than LNF (Broeders et al. 2009b; Salminen et al. 2012).

2.7.3 LNF vs. ONF

There are two RCTs with long-term follow-up comparing LNF and ONF.

Broeders and colleagues published an RCT with ten-year results comparing LNF and ONF. The study group consisted of 177 PPI-refractory patients, 79 (81%, LNF) and 67 (85%, ONF) of whom participated. The operative technique consisted of a floppy 2.5–3.0 cm long 360° wrap after the division of SGVs, full mobilization of the esophagus, and posterior hiatoplasty. The symptomatic outcomes of the groups were statistically similar regarding heartburn (no or mild, 94.9% LNF vs. 91.1% ONF) and dysphagia (no or mild, 92.4% LNF vs. 85.1% ONF), while LNF relieved regurgitation more efficiently (no or mild, 98.7% LNF vs. 91.0% ONF). There was no significant difference between the groups in the improvement and state of their quality of life, readiness to choose surgery again (78.5% LNF vs. 72.7% ONF), and the use of acid suppressing drugs (26.6% LNF vs. 22.4% ONF). There were six (7.6%) conversions in the LNF group. The risk for surgical re-intervention was higher in the ONF group, as 15.2% (n=12) and 34.8% (n=24) of patients underwent a re-intervention in the LNF and ONF groups, respectively. Furthermore, 2.5% (n=2) and 13.4% (n=9) of the patients in the LNF and ONF groups, respectively, were re-operated on because of an incisional hernia. (Broeders et al. 2009b.)

Another RCT with long-term results (median follow-up 15.1 years) comparing the two techniques reported objective results achieved by means of endoscopy. At baseline, 110 ERD patients were randomized to LNF or ONF groups. The operative technique varied to some extent, as SGVs were ligated in five operations in both of the groups and hiatoplasty was performed on four patients in the LNF group and one in the ONF group. Eighty-six patients (LNF 87%, ONF 69%) participated, and 64 (71.9%) underwent endoscopy. There were no statistically significant differences in symptomatic outcome between the two groups. No or mild heartburn or regurgitation was reported by 77.1% and 76.3% in the LNF and ONF groups, respectively. No or mild dysphagia was reported by a respective 91.7% and 89.5%. Moderate to severe bloating and flatulence was reported by 79.1% in the LNF and by 71.1% in the ONF group. PPIs had been used by 46.5% of the patients in the whole study cohort, while 15.1% needed PPIs on a daily basis. In the LNF group, the patients were more satisfied with the surgical result, as 91.7% gave a positive evaluation vs. the 76.3% in the ONF group, and 77.1% would have chosen surgery again in the LNF group as opposed to the 65.8% in the ONF group. Significantly more fundoplication wraps were observed to be defective in the ONF (46.4%) group than in the LNF (11.1%) group. Defective wraps were associated with PPI use, heartburn, and regurgitation, and with a negative evaluation of the result of surgery. Intact wraps were associated with bloating and flatulence. Three conversions (6.2%) were made. There were no incisional hernias in the LNF group, while the hernia rate in the ONF group was 25%. The reoperation rate was 7.3% in the ONF group and 5.5% in the LNF group (Salminen et al. 2012). From the same series, results have also been reported 11 years postoperatively (Salminen et al. 2007).

The patient satisfaction seems to be higher after LNF than after ONF, and incisional hernias after open operations raise the risk of reoperations related to ONF.

2.7.4 LNF or ONF vs. medical treatment

There are three RCT series comparing the results of LNF and PPIs in the treatment of GERD with three to seven years of follow-ups.

In a multicenter RCT conducted in 11 European countries (the LOTUS study), a standardized LNF was compared to an adjusted dose of esomeprazole in patients initially responsive to PPI treatment. Five-year follow-up results have been published. At five years, the participation was 73% (n=180) in the surgical group and 72% (n=192) in the medical group. An estimated 85% of surgical patients and 92% of medically treated patients remained in remission. The remission rate in the LNF group deteriorated slightly between three (90%) and five years. A need for acid-suppressive drugs, newly-onset symptoms needing intervention, and reoperations were classified as treatment failures in the surgical arm, while an insufficiency of esomeprazole 40mg/day to control heartburn or regurgitation was considered a failure in the medical arm. The operated patients had less heartburn (not significant) and regurgitation while medically treated patients had less dysphagia, flatulence, and bloating. HRQoL was measured using the Quality of Life in Reflux and Dyspepsia and the Gastrointestinal Symptom Rating questionnaires. In both groups, the mean scores for all dimensions improved and remained close to the values of a healthy population. There was no mortality caused by the treatments, and the safety profiles were similar (Galmiche et al. 2011).

Anvari et al. published an RCT comparing patients with long-term GERD medication three years after randomization to LNF or optimized medical therapy. They recruited 104 patients with excellent symptom control and a continuous use of PPI for at least one year. At three years, the follow-up rates were 88% for the PPI group and 96% for the surgical group. Both groups had similar and significantly better control of reflux symptoms. In the surgical group, patients experienced significantly more heartburn-free days. Both groups improved in the 24h pH monitoring, and there was no significant difference between the two, albeit acid exposure was normalized in the surgical group, whereas that of the medical group remained pathological. The global symptom control measured using VAS and the quality of life measured using the SF-36 improved more and were significantly better in the surgical group. The rates of treatment failure were 11.8% and 16% in surgical and medical groups, respectively. All six patients whose treatment failed in LNF group resumed PPI therapy, and four were re-operated on. Eight patients in the medical group underwent LNF due to PPI failure. There were no intraoperative complications nor major morbidity or mortality. Four LNF patients had dysphagia, and seven reported bloating at three months. No adverse events were reported in the medical group (Anvari et al. 2011).

In an RCT by Mehta et al., 183 patients with an at least six-month symptom history, and a minimum of three months' PPI therapy and objectively verified GERD, were randomized to either the PPI (n=92) or the LNF (n=91) group. After 12 months, the PPI-treated patients were given a chance to have surgery. A further 54 patients chose to undergo LNF, which left 38 patients in the PPI group. After a follow-up of a median of 6.9 years, a questionnaire was sent to the patients and 79% responded. There was a significant reduction in symptom scores in both the surgically and the medically treated, as well as in those who chose surgery at one year. Of those who remained on PPIs, 59% were very satisfied compared with 80% of the surgery group. There were no conversions or mortality. Two patients suffered an esophageal injury and two patients a splenic injury, which were all managed laparoscopically and caused no postoperative sequelae. During the early recovery period, four patients had dysphagia requiring dilation, and two patients had wrap migration and a reoperation. In the PPI group, 10% of the patients had side effects, such as headache, diarrhea, vomiting, or abdominal pain, which required a change of the PPI (Mehta et al. 2006).

The only RCT with long-term results comparing surgical and medical treatment reports the outcome of ONF and omeprazole treatment at twelve years. Only 37% (n=53) of patients in the surgical group and 46% (n=71) in the medical group were available for follow-up. The patients included had ERD at baseline. The patients treated surgically had significantly less heartburn and regurgitation than those treated with omeprazole, whereas dysphagia, flatulence, impaired belching, and inability to vomit were significantly more common in the surgery group. In 38% of the patients treated surgically, medical treatment or another operation were also required, whereas a change in therapeutic strategy was noted in 15% of the medically treated patients. Twenty-one of the 155 (14%) patients originally treated with PPIs were referred for operative treatment. The GSRS and Psychological and General Well-Being Index gave similar scores for both groups, and the scores were comparable to those of a normal population. There was no treatment-related mortality. One patient in the fundoplication group developed esophageal cancer (Lundell et al. 2009).

A recent Cochrane review comparing laparoscopic fundoplication and medical treatment found four RCT series which were accepted in the study. In addition to the above-mentioned studies, a report by Grant et al., which also includes partial fundoplications, was included. It was concluded that a smaller proportion of patients suffer from the typical symptoms of GERD (heartburn and regurgitation) after surgical treatment than after medical treatment, while the proportion of patients with serious adverse events and dysphagia was higher after surgery. It was noted that the grading of symptoms was inadequate. In the balance of benefits versus harms considerable uncertainty remained between laparoscopic fundoplication and PPIs (Garg and Gurusamy 2015).

2.7.5 LNF in low-volume centers and at the general level

Most of the studies reporting results of antireflux surgery are from highly specialized centers, but a significant proportion of the operations are performed at the general level in smaller hospitals, which may not be as specialized as the high-volume centers, or the operation rates are lower (Sandbu et al. 2002; Varban et al. 2011; Viljakka et al. 1997). There are five studies from the US and one study each from Sweden and Norway investigating the national LNF results outside the high-volume centers. Only the Norwegian study provides a long-term follow-up.

The study by Vakil et al. found the results from low-volume centers of US communities to be poorer than what has been reported from the referral centers, as only 61% of the patients were completely satisfied and 67% reported newly-onset symptoms after the operation. Also, the symptomatic outcome was suboptimal. It was found that many of the patients had false expectations concerning the operation, and the need for adequate patient education and informing was noted (Vakil et al. 2003). In a study comparing high- and low-volume centers in North Carolina, it was observed that, even though low-volume centers perform LNF on younger patients with less comorbidities, low-volume centers had more intraoperative punctures or lacerations (3.3% vs. 0.9%). There was no mortality or difference in the median length of hospital stay (Varban et al. 2011).

The studies by Ranson et al. and Tucker et al. demonstrated that, with an adequate preoperative work-up and dedication to LNF, results comparable to those from referral centers can be achieved at a general level (Ranson et al. 2007; Tucker et al. 2005). Good results have also been documented from low-volume centers by using a standardized preoperative examination protocol and operative technique (Kornmo and Ruud 2008; Xenos et al. 2001).

Somewhat conflicting results were reported in a Swedish study comparing the results of high- and low-volume hospitals (≤ 8 operations per year). The patients of high-volume centers had more postoperative heartburn (11.0% vs. 6.8%), regurgitation (8.6% vs. 5.3%), dysphagia (10% vs. 9.1%), and dissatisfaction with the procedure (15% vs. 13.9%), and they were re-operated on more often (6.0% vs. 2.9%), whereas the patients of low-volume centers reported more operation-related side effects, such as difficulties in belching (46.0% vs. 29.0%), difficulties in vomiting (55.3% vs. 39.0%), and daily complaints of gas-bloat symptoms and flatulence (39.1% vs. 31.8%). None of the variables reached statistical significance. Medication was used at least once a week by 19.5% and 11.1% of patients in the high- and low-volume groups, respectively (Sandbu et al. 2002).

The quality of the studies reporting LNF results from low-volume centers is variable. None of the studies reported objective outcomes. On the basis of subjective outcomes, it seems that, with an appropriate pre-operative work-up and correct indications, adequate results may be achieved at a general level and even in low-volume centers. On the whole, the reported surgery-related complications are rare. Postoperative symptoms are variably described, and some studies lack the description of the operative technique, but it seems

that treatment-related side effects are a major complaint (Kornmo and Ruud 2008; Ranson et al. 2007; Sandbu et al. 2002; Vakil et al. 2003), which may, in part, be a consequence of issues with the indications. The application of a technique with the division of the SGVs (Kornmo and Ruud 2008; Ranson et al. 2007; Tucker et al. 2005; Xenos et al. 2001) may also increase the side effects (Engstrom et al. 2011). The infrequency of the operations may drive a surgeon to perform the division of the SGVs in order to achieve a loose enough wrap more easily.

2.7.6 LNF in the elderly

The safety of the surgical treatment of GERD in the elderly has been contemplated on. The two studies comparing older and younger patients (≥ 65 or 18–64 years in the study by Fei et al.; >70 or ≤ 70 years in the study by Wang et al.) found a similar subjective outcome between the groups, and in the study by Fei et al., there was also no difference in objective outcome measures. There was no mortality, and no conversions were done, and the only difference in the complications was observed in the study by Wang et al., in which three patients (9%) in the elderly group had a minor complication (2 cases of pneumonia and 1 dysphagia with no revision required), whereas in the younger age group, one (0,5%) patient had a subcutaneous emphysema (Fei et al. 2013; Wang et al. 2008).

A prospective study by Grotenhuis et al. compared operative treatment of large paraesophageal hernias ($n=129$) and GERD ($n=81$) in patients ≥ 70 years of age. LNF was performed on 40% of the patients, whereas the rest underwent a partial fundoplication. The intraoperative complication rates were 7.0% and 3.7% for the hernia and GERD groups, respectively, and the respective postoperative complication rates were 10.1% and 4.9%. Two patients in the hernia group died perioperatively: one because of septic shock caused by an esophageal perforation and the other because of cardiac failure after a myocardial infarction. The reoperation rate and satisfaction with the treatment as well as the use of postoperative medication were comparable to the literature (Grotenhuis et al. 2008).

It seems that the risk of complications is slightly increased in the elderly, whereas the results concerning reflux control are comparable to the younger patients. To prevent postoperative dysphagia in the elderly, a partial fundoplication has been proposed to be used (Broeders et al. 2013).

2.7.7 Antireflux surgery and Barrett's esophagus

The possible ability of antireflux treatments to prevent BE from developing into EAC is an important subject, but a hard one to study.

The loss of short-segment IM has been reported in 27.3%–61% of patients after LNF (Csendes et al. 2009; Oelschlager et al. 2003; Zaninotto et al. 2012), whereas none of

the patients with long-segment metaplasia regressed in the studies by Oelschlager and Zaninotto (Oelschlager et al. 2003; Zaninotto et al. 2012). The overall rate of complete loss of IM was 17% in the review by Chang et al. after surgical treatment (Chang et al. 2007). In a Finnish population-based study from 1980 to 2006, 5.1% of EAC patients had been operated on because of GERD. In patients with an intact fundoplication, EAC had developed at a mean interval of 6.4 years, whereas in those with a failed fundoplication, the interval was significantly longer (11.2 years). Only 30% of EAC patients had a normal function of the fundoplication (Kauttu et al. 2011). It has been proposed that, if genetic alterations have already taken place at the time of surgery, the cancer occurs within the first postoperative years, while a later-developing cancer might associate with a failure of the fundoplication (DeMeester 2015; Kauttu et al. 2011).

There is only one RCT comparing medical and surgical treatment of Barrett's esophagus with IM. No difference was found between the treatments in preventing BE from progressing into dysplasia and EAC after a median follow-up of 5 years in the medical group and 6 years in the surgical group, but only one low-grade dysplasia was found among the patients with an intact fundoplication. There were no cases of complete regression of IM. The incidences of EAC were 0.8% and 0.5% per year in the medical and surgical groups, respectively (Parrilla et al. 2003). Zaninotto et al. also reported better results after successful LNF than after PPIs as far as a higher intestinal metaplasia reversion rate in short-segment BE is concerned, but not with long-segment BE (Zaninotto et al. 2012).

In a systematic review-article by Chang et al. comparing the incidence rates of EAC in patients with Barrett's esophagus and treated with antireflux medication or surgery, no convincing difference was found. The review consisted of various surgical treatments, and the heterogeneity in the incidence of EAC among surgically treated patients between different types of studies was considered to be possibly due to publication or inclusion biases (Chang et al. 2007).

In summary, LNF does not seem to prevent the development of EAC, but there is some evidence suggesting that an intact fundoplication might reduce the risk of malignancy. The low incidence of EAC makes the conduction of adequately powered studies difficult. It seems that a well-functioning fundoplication promotes the regression of intestinal metaplasia, while the diagnosis between dysplasia and inflammation is a confounding factor (Chang et al. 2007; DeMeester 2015).

2.7.8 LNF in NERD patients, LNF and non-acidic reflux

There are two comparative studies with mid-term follow-up confirming equal results after fundoplication for NERD and ERD patients with objectively verified GERD, and one study suggesting similar results for patients with esophageal acid hypersensitivity (Broeders et al. 2009a; Broeders et al. 2010b; Kamolz et al. 2005). Also, good results have been reported with negative pH monitoring but a positive total number of reflux episodes or positive SI

detected with MII-pH (del Genio et al. 2008). In the short term, it has been reported that Nissen fundoplication markedly decreases acidic, weakly acidic, duodenogastroesophageal, liquid, and mixed refluxes (Broeders et al. 2011a; Elhak et al. 2008). The decrease in gas reflux was also statistically significant, but less prominent after LNF with a division of SGVs (Broeders et al. 2011a). The established reflux-symptom correlation seems crucial in order to achieve successful results, as poorer results have been reported in the case of no confirmed relation (Khajanchee et al. 2004).

2.7.9 LNF vs. partial funduplications

2.7.9.1 LNF vs. partial posterior fundoplication

There is one RCT comparing LNF and laparoscopic posterior 270° fundoplication (Toupet, LTF) with follow-ups of 5.0 and 4.6 years for each group, respectively. One hundred patients with PPI-dependent ERD or with objectively verified PPI-resistant GERD were included. The operation included routine hiatoplasty and the division of SGVs. In the LNF group, higher postoperative wrap pressure (15.28mmHg vs. 12.07mmHg) and increase in LES pressure (11.9mmHg vs. 5.3 mmHg) were measured. There were no differences in the results of 24h pH monitoring. There were no statistically significant differences between the two groups in any symptoms at any point, with the exception of higher preoperative bloating in the LTF group. The results for pre- and postoperative esophageal dysmotility or dysphagia were similar. Recurrent GERD symptoms developed in 16.84% (n=16) of the patients, eight patients in each group. The groups were equally satisfied with the results of surgery. There were no conversions. The overall revision rate was 7.4%. The reasons for revision in the LNF group were: recurrent GERD in 1, dysphagia in 2, and slipped wrap in 1 case. All the three revisions in the Toupet group were made due to recurrent GERD (Shaw et al. 2010).

A long-term follow-up RCT comparing ONF and open Toupet fundoplication with a mean follow-up of 18 years has been published. Follow-up data was obtained for 53.3% (n=73) of the original study population. There was no difference between the groups in the scores for heartburn, regurgitation, dysphagia, gas bloating, and flatulence. It was noted that the treatment-related side effects, such as bloating and flatulence, improved over time in the ONF group (Mardani et al. 2011).

In a systematic review and meta-analysis comparing LNF and LTF, it was suggested that LTF reduces dysphagia and the need for dilatation, and gas-related symptoms and re-operations were more common after LNF, while reflux control between the techniques was similar. The respective rates of postoperative dysphagia and dilatation were 13.5% vs. 8.6% for LNF and 6.9% vs. 2.7% for LTF. The number of surgical re-interventions was 7.0% vs. 3.1%. The higher number of surgical re-interventions in the LNF group was explained by the higher incidence of postoperative dysphagia. The review included seven RCTs with

relatively small numbers of patients each, and the follow-up periods were restricted to 1 year (n=4), ~2 years (n=2), and to five years in one (Broeders et al. 2010a). It has been noted that the treatment-related side effects diminish over time after Nissen fundoplication (Broeders et al. 2011b; Broeders et al. 2013; Mardani et al. 2011; Salminen et al. 2012), so it can be expected that the advantage of LTF in light of side effects may diminish with the length of follow-up. In addition, although the in-hospital complications were statistically similar, there were three esophageal perforations after LTF and none after LNF. The greater number of esophageal sutures in LTF may increase the risk for esophageal perforation (Broeders et al. 2010a).

2.7.9.2 LNF vs. partial anterior fundoplication

There are two RCTs with long-term follow-up comparing the results of LNF and laparoscopic partial anterior fundoplication (LAF).

Djerf et al. reported the results of a multicenter RCT concerning LNF vs. laparoscopic anterior 120° fundoplication after a median follow-up of 10.1 years. Seventy-two patients with objectively verified PPI-responsive GERD were randomized to the two groups. Posterior hiataloplasty was performed on all of the patients, while division of the SGVs was not performed in the LAF group and, in LNF group, the division was performed when needed. A respective 32 (89%) and 29 (81%) patients in the LNF and LAF groups participated at ten years, and a total of 30 patients underwent pH and endoscopy studies. One patient in the LNF group underwent conversion because of adhesions and subsequently developed an incisional hernia. There were neither reoperations nor any difference in heartburn, regurgitation, dysphagia, or flatulence between the groups during the first year, but more patients in the LAF group were able to belch at one year. After ten years, the LAF group had a higher incidence of heartburn, while the symptom levels in both the groups were modest. In addition, the LAF group reported less flatulence and dysphagia, and more patients were able to belch and vomit at ten years. Dysphagia increased in the LNF group between 1 and 10 years. At ten years, 25% and 34% of the patients in the LNF and LAF groups, respectively, used PPIs daily or weekly. At 1 year, 14.2% in the LAF group and 3.3% in the LNF group had erosive esophagitis, while, at ten years, only one patient in the LAF group had Grade A esophagitis. All patients in the LNF group (n=13) had endoscopically intact wraps, while three wraps (17.6%) in the LAF group (n=17) were defective. In 24h pH monitoring, a higher acid exposure was recorded in the LAF group at one year, although the results were within the normal range in both groups. There was no difference between the groups in 24h pH monitoring at ten years. There were no differences in quality of life between the groups as measured using the Psychological General Well-Being index (Djerf et al. 2016).

The longest follow-up comparing LNF and laparoscopic partial fundoplications is reported by Broeders et al. in a study comparing LNF and laparoscopic anterior 180°

partial fundoplication after 14.0 and 14.2 years, respectively. Originally, 103 patients with objectively verified GERD were enrolled, and early results were published. For the long-term follow-up, all patients who had not undergone a re-operation were invited to participate, and subjective and objective results were obtained if the patient was compliant. In the LNF group, 46 (86.6%) patients were available for subjective measuring and 10 patients for subjective and objective measuring. The corresponding numbers for the LAF group were 41 (75.9%) and 8. Patients in the LAF group more frequently suffered from heartburn, while patients in the LNF group were more likely to have dysphagia for solids but not for liquids and the overall dysphagia was higher. There was an increasing trend in the heartburn scores of the LAF group after five years. There was no difference in bloating, inability to belch, or inability to relieve bloating, and the gas reflux, gastric belches, or belches experienced by the patients were also the same between the groups, suggesting that the short-term differences in gas reflux disappear over time. There was no difference in patient satisfaction during the follow-up. More reflux episodes were detected in the LAF group. One out of 8 patients in the LAF group and 7 out of 10 in the LNF group had no esophageal acid exposure. The LES pressures were lower in the LAF group (Broeders et al. 2013).

In a meta-analysis comparing LAF to laparoscopic posterior fundoplications (Nissen and Toupet), it was found that LAF had lower dysphagia scores, while the posterior fundoplications were associated with better heartburn control on a short- and medium-term basis when compared to LAF. The authors concluded that the posterior fundoplications are better alternatives to LAF for controlling GERD symptoms (Memon et al. 2015).

The results after LNF and partial fundoplications are close to being similar. LNF seems to offer a more extensive relief of typical GERD symptoms, but dysphagia is reported more often in connection with LNF than partial fundoplications. Broeders et al. suggested LNF for younger patients to ensure durable reflux control and LAF for older patients to minimize dysphagia (Broeders et al. 2013).

2.7.10 The durability of LNF wraps, the long-term results of LNF in routine clinical practice, and the possible lifelong relief of reflux symptoms after Nissen fundoplication

In general, the treatment of GERD aims to enhance the patients' quality of life. The prevailing surgical treatment, Nissen fundoplication, is an invasive procedure, which alters the anatomy of the GEJ irreversibly. High numbers of endoscopically detected defective fundic wraps have been reported after ONFs, but the knowledge concerning the durability of the wraps after LNF has been scarce (Luostarinen et al. 1993b; Rantanen et al. 1999; Salminen et al. 2012). Most of the studies reporting results of antireflux surgery are from highly specialized centers, but a significant proportion of the operations are performed at a general level in smaller hospitals (Sandbu et al. 2002; Varban et al. 2011; Viljakka et

al. 1997). There are few studies reporting long-term results from routine clinical practice, and the longest follow-ups in the reports are limited to 20 years (Luostarinen et al. 1993b; Robinson et al. 2015). The pragmatic long-term follow-up results of LNF as well as the extremely long-term follow-ups mimicking the lifelong results of Nissen fundoplication have been lacking.

3 AIMS OF THE STUDY

The aims of this study were to analyze the long-term results of LNF in routine clinical practice and to estimate the lifelong symptom control of Nissen fundoplication, in addition to studying the impact of the introduction of LNF on the surgical treatment of GERD.

The specific aims were as follows:

1. To describe the indications, operative technique, and annual rates of antireflux surgery in Kanta-Häme Central Hospital after the adoption of the laparoscopic technique.
2. To define the long-term results of LNF with regard to health-related quality of life ten years after the operation.
3. To study the long-term durability of the surgical results of LNF in routine clinical practice ten years after the operation and to depict the subjective outcomes as well as the impact of fibrin glue on the incidence of surgical failure.
4. To present almost lifelong follow-up (>30 years) after ONF in terms of subjective outcomes and health-related quality of life and to describe the indications for antireflux surgery before the laparoscopic era.

4 MATERIALS AND METHODS

The study populations consisted of two branches. The first branch included patients operated on at Kanta-Häme Central Hospital between 1991 and 2000, and the second branch consisted of patients operated on at Tampere University Hospital between 1983 and 1984. The profiles of the studies are illustrated in Figure 5, and the patient characteristics are described in Table 5.

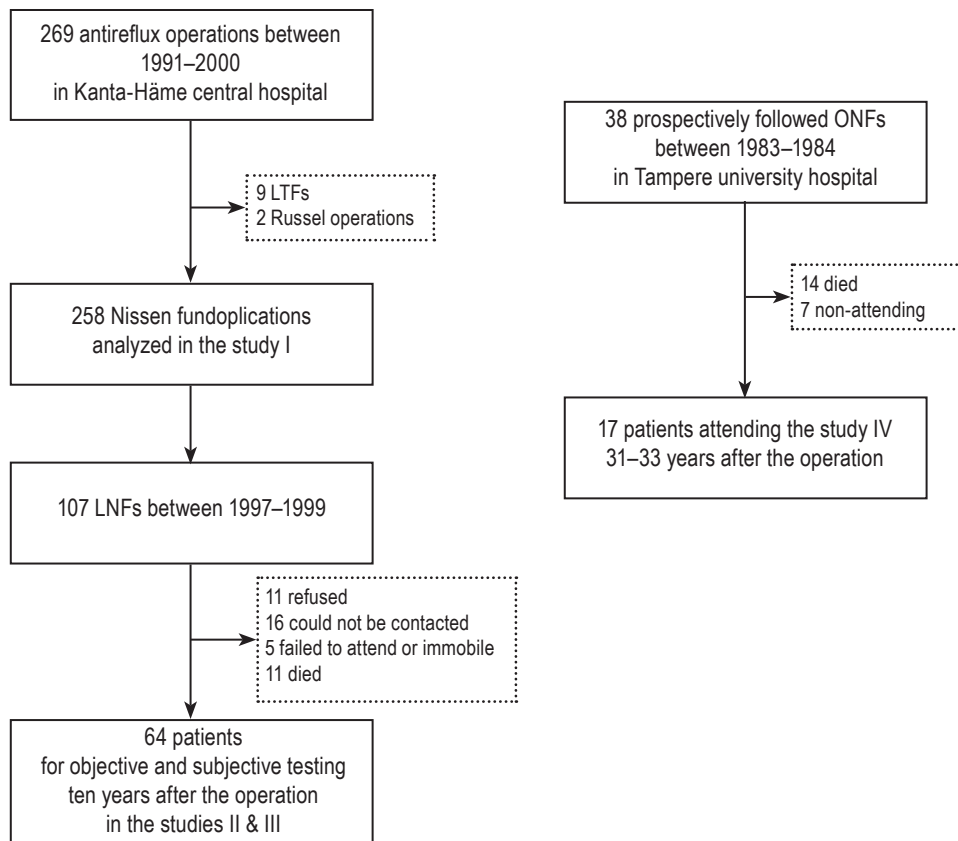


Figure 5. Study profiles

Table 5. Patient characteristics

Characteristic	Study I	Studies II–III	Study IV
Mean age at operation (years)	53	52	43
Male gender (%)	58	63	47

4.1 The impact of fibrin glue in the prevention of failure after Nissen fundoplication (I)

In Kanta-Häme Central Hospital, 269 patients were operated on for GERD in 1991–2000. Our analysis (in study I) focused on Nissen fundoplications, the number of which during the same period was 258. The preoperative symptoms, antireflux medication, and demographic data of the study population as well as the details of the operation were collected retrospectively. Peri- and postoperative complications, complaints, and symptoms were recorded. The information from the routine outpatient clinic visits was analyzed. Pre-, peri- and postoperative data was collected from hospital records using a structured form drawn up by the authors.

4.2 Health-related quality of life 10 years after laparoscopic Nissen fundoplication – results of a community-based hospital (II) & endoscopic evaluation of laparoscopic Nissen fundoplication: 89 % success rate 10 years after surgery (III)

In the 1990s, the use of the laparoscopic technique gradually became more common in the Kanta-Häme Central Hospital, and the year 1996 was the first when the majority of the operations were LNFs. To avoid a possible learning curve bias, we focused on the following three-year period (1997–1999) for studies II and III. With partial and open fundoplications excluded, but laparoscopic procedures which had been converted included, the total number of LNFs during the three years was 107.

All patients were mailed a form consisting of questionnaires with symptom scores and a HRQoL instrument. The patients who participated were interviewed in 2008–2009 by a nurse who had not previously taken part in the treatment of the patients. The form was filled out in collaboration with the nurse.

The HRQoL was measured using a multidimensional generic 15D instrument, and a comparison was made between our patient group and an age- and sex-standardized general Finnish population. The 15D dimensions are: vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. The valuation system of 15D is based on an application

of the multi-attribute utility theory. The 15D score, representing the overall HRQoL on a 0–1 scale (1 = full health, 0 = being dead), and the dimension level values, reflecting the subject's reported level relative to no problems in the dimension (=1) and to being dead (=0), are calculated from the health state descriptive system using a set of population-based preference or utility weights. (Sintonen 2001.)

To evaluate heartburn, regurgitation, and dysphagia, the four-point (none, minimal, moderate, severe) DeMeester-Johnson reflux scale was used (Demeester et al. 1976). Bloating and flatulence were assessed using a similar four-point scale. With every symptom, the preoperative and the current condition was evaluated.

The satisfaction level with the preoperative condition and with the results of surgery was graded as satisfied, undecided, and unsatisfied. The patients evaluated whether they would still undergo surgical treatment with the benefit of hindsight.

The postoperative use of antireflux medication and postoperative interventions, such as esophageal or pyloric dilatations and re-operations due to failed antireflux surgery or wound problems, were gathered.

Upper gastrointestinal endoscopy was performed on the patients by two of the authors after the interview. The endoscopists did not know the results of the interview when performing the endoscopy. The appearance of the fundic wrap was noted along with esophagitis, macroscopically metaplastic areas, and hiatal hernia. The fundic wrap was classified as defective if a distinct gastric pouch above the narrowing caused by the folds of the wrap could be observed (Slipped Nissen), or if there were no visible folds (total disruption) or only distorted, loose folds (partial disruption) at the GEJ. If a gap was found beside the fundic wrap, a recurrent hiatal hernia was recorded and classified. A defective fundic wrap was classified as a surgical failure. All the wraps were photographed, and the photographs were analyzed later in conjunction with the other authors.

4.3 Does Nissen fundoplication provide lifelong reflux control? Symptomatic outcome after 31–33 Years (IV)

Between January 7, 1983, and November 6, 1984, single surgeon's 38 consecutive patients underwent ONF at Tampere University Hospital. On December 7, 2015, the hospital records of the patients were reviewed to gather information for study IV about the preoperative evaluation, symptoms, indications for surgery, and the operative technique. The medical history concerning GERD was examined, and re-interventions and complications (reoperations, endoscopies and incisional wound issues) were searched for. Death certificates for the 14 patients who had died were requested from Statistics Finland.

Questionnaires were sent to the 24 patients still living regarding symptoms, satisfaction, HRQoL, antisecretory medication use, and further interventions. When not returned, the questionnaires were resent a further two times.

The symptom ratings were accomplished with the GSRS, the Visick score, VAS (bloating and flatus), and the DeMeester-Johnson reflux scale (heartburn, regurgitation, and dysphagia). New-onset symptoms after the procedure were inquired about. The GSRS consists of 15 items of gastrointestinal symptoms, which are further divided into five clusters. The five clusters consist of gastroesophageal reflux, abdominal pain, indigestion, diarrhea, and constipation. Each item of the GSRS has a seven-point Likert-type scale where 1 represents the absence of bothersome symptoms and 7 represents very bothersome symptoms (Revicki et al. 1998b). The Visick score is a four-point scale to assess the effect of the treatment (1, no symptoms – resolved; 2, mild occasional symptoms easily controlled – improved; 3, mild symptoms not controlled – unchanged; 4, not improved – worsened) (Visick 1948). The VAS gives points from 0 (normal) to ten (worst possible symptoms) (Reading 1989). To simplify the comparisons between different symptoms, the VAS values were converted into a four-point symptom severity scale as follows: 0=none, 1-33=minimal, 34-66=moderate and 67-100=severe.

The HRQoL was evaluated using the 15D instrument (Sintonen 2001).

The patients were requested to define both the preoperative and the current situation with regard to every symptom and instrument.

The satisfaction levels with the preoperative condition and with the results of surgery were stated as satisfied, undecided, or unsatisfied, and the willingness to choose operative treatment again in retrospect was inquired about.

5 STATISTICAL ANALYSIS

(I) Univariate analysis using a Chi-square test was made for statistical comparisons. A multiple logistic regression model was used to identify independent factors related with failure. (II) The differences between the two groups' mean (median) 15D scores and dimension level values were tested using the Mann-Whitney U test. To explore the extent to which a lung disorder and dissatisfaction with the results of surgery might affect the 15D score, a regression model was run with the 15D score as the dependent variable and age, sex, lung disorder, and dissatisfaction with the results of surgery as explanatory variables. (III) The comparisons between pre- and postoperative symptoms and satisfaction levels with the treatment were made using a marginal homogeneity test. The relationship between surgical failure and other variables were estimated using the Linear-by-Linear association test. The Chi-square test was used to search associations between postoperative PPI use and explanatory factors. (IV) A marginal homogeneity test was used to calculate statistical significance between pre- and postoperative values as regards heartburn, regurgitation, dysphagia, and Visick score. A pairwise T test was applied to evaluate GSRS and 15D mean values. The Wilcoxon test was applied when analyzing the VAS data. The values of 15D data were assessed with the Mann-Whitney U test. P-values less than 0.05 were considered significant. Statisticians outside the research group were used to run the statistics.

6 ETHICAL CONSIDERATIONS

Patients recruited for the study signed an informed consent. Studies I–III were approved by the Ethical Committee of Kanta-Häme Central Hospital (Dnro e7/2002 and Dnro 414/2007). Study IV was approved by the Ethical Committee of Kuopio University Hospital (Dnro 381/2015).

7 RESULTS

7.1 The Impact of fibrin glue in the prevention of failure after Nissen fundoplication (I)

In 1991–2000, the patients enrolled in study I were operated on only due to objectively verified GERD at Kanta-Häme Central Hospital. Of the patients, 70% had ERD, and 91% of 24h pH monitoring studies showed pathological acid exposure. The preoperative work-up consisted of pH monitoring (86.8%), manometry (78.8%), and either endoscopy (99.2%) or a barium esophagram (0.8%).

The 258 operations were performed by 12 different surgeons, and a significant increase in the total number of operations per year ($p=0.034$) was noted. There were 201 LNFs and 57 ONFs during the study period. The first LNF was performed in 1994, and the number of LNFs increased until peaking at 49 operations in 1998. The wrap was calibrated with a nasogastric tube (52%), an endoscope (17.8%), or an either 48 or 52 French bougie (30.2%). The division of SGVs was carried out in 22.5%, hiatoplasty in 53%, and anchoring of the wrap in 76% of the patients. Fibrin glue was used to strengthen the wrap in 53.5% of the cases. The use of a fixation suture of the wrap ($p=0.002$) and hiatoplasty ($p<0.001$) increased markedly over the study period (Figure 6).

The mean follow-up was 61.5 months (range 21–137 months). Recurrent esophagitis, a defective fundic wrap, or recurrent hiatal hernia was detected in 14.9% of the patients during the routine outpatient clinic control visits. There was no difference between the ONF (15.8%) and LNF groups (8.5%). The conversion and reoperation rates were 11.9% and 3.9%, respectively. In multivariate analysis, hiatoplasty ($p=0.010$) and fibrin glue ($p=0.019$) were found to be independent factors decreasing the incidence of failure, when failure was defined as recurrent esophagitis or defective wrap. The wrap failure rates in relation to the use of fibrin glue are presented in Table 6.

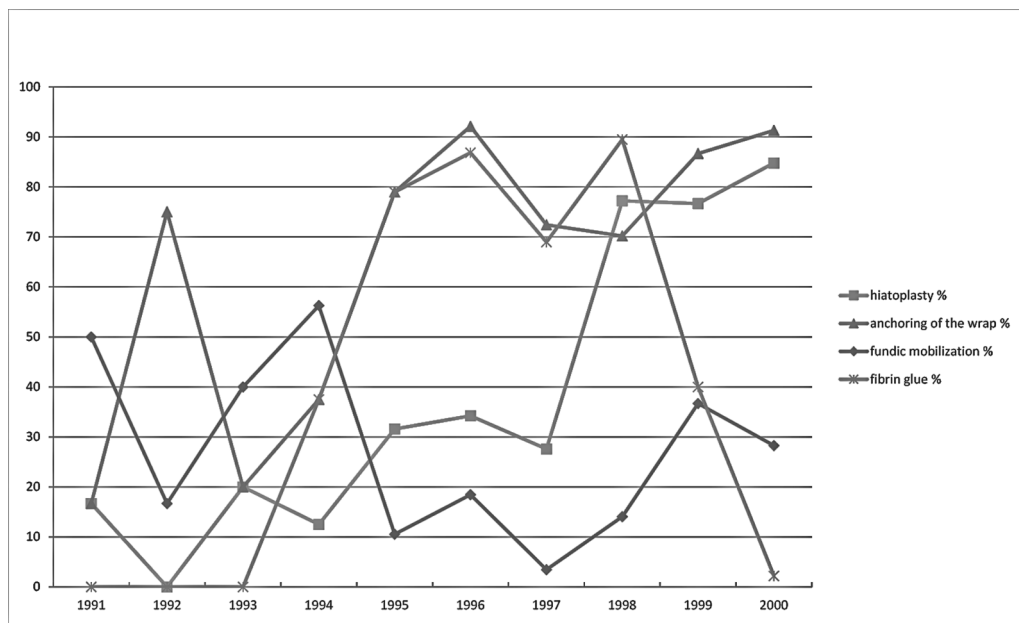


Figure 6. The annual percentages of the use of hiatoplasty, anchoring of the wrap, fundic mobilization, and fibrin glue

7.2 Health-related quality of life 10 years after laparoscopic Nissen fundoplication – Results of a community-based hospital (II)

The participation rate in study II was 59.8% (64 out of 107 patients). The participation rate of the still-living patients was 66.7%. The mean follow-up time was 9.8 years. The review of patient records revealed no late complications or re-operations among the 43 non-participating patients. Nine patients (14.1%) reported having a lung disorder, the prevalence of which is higher than what is found in the general Finnish population. Otherwise, the morbidity was comparable to the general population.

Preoperatively, 90.6% had been unsatisfied with their condition, while only 6.3% were unsatisfied with the results postoperatively. Dysphagia was the most common reason for discontent.

The mean 15D score of our patient group was 0.860, whereas the mean score for the age-standardized general population was 0.888 ($p=0.030$). The mean 15D scores, as well as the scores in any of the individual dimensions, were similar between men and women. The mean values of patients for breathing, sleeping, excretion, discomfort and symptoms, and depression were lower, and the values for vision were higher than those of the age-standardized general population. Additionally, there was a statistically significant difference in the median level value for the dimensions of eating, distress, and vitality. The

mean 15D score of the satisfied patients was 0.870 (median 0.890), which is clinically the same as that of the general population.

A lung disorder decreased the mean 15D score by 0.068 ($p=0.039$), and dissatisfaction with the treatment decreased the mean 15D score by 0.069 ($p=0.023$). Thus, subjective failure of the treatment was found to be a reducing factor in HRQoL.

7.3 Endoscopic evaluation of laparoscopic Nissen fundoplication: 89 % success rate 10 years after surgery (III)

The study population of study III consisted of the same patients that were enrolled in study II.

A defective wrap was found in seven (10.9%) endoscopies. A slipped Nissen was detected in six patients and a wrap disruption in one. A defective wrap was classified as surgical failure. Surgical failure was more prevalent if fibrin glue was not used (Table 6; $P= 0.036$). The wrap was not fixed in two and fibrin glue was not applied in four out of the six cases with a slipped Nissen. One slipped Nissen had occurred despite the fixation and the use of fibrin glue.

Table 6. The wrap failure rates with and without fibrin glue

Study	I	III
wrap failure rate with fibrin glue %	6	6
wrap failure rate without fibrin glue %	8	29

The reoperation rate was 4.7% ($n=3$). Two of the reoperations were performed for an endoscopically verified slipped Nissen and symptom recurrence, and one because of dysphagia and weight loss. The dilatation rate was 7.8%. One patient had a dilatation for ventricle retention (pyloric dilatation). No dilatations had been performed on the non-attending patients in our hospital. Three patients had undergone a postoperative hernia repair (4.7%). The postoperative use of antisecretory medication was 26.6%, whereas 9.4% of the patients were on continuous medication. A correlation was found between the use of antisecretory medication and surgical failure ($p=0.025$), but not with the prevalence of esophagitis ($p=0.099$).

No or only minimal heartburn was reported by 90.6% ($p<0.001$; Figure 7) and no or only minimal regurgitation by 95.3% ($p<0.001$; Figure 8) of the patients. The patients with a defective wrap had more heartburn ($P=0.004$) and regurgitation ($P=0.012$) than those with an intact fundoplication wrap. An increase in dysphagia was noted ($p=0.026$; Figure 9)—64.1% of the patients reported no or only minimal dysphagia, 32.8% had moderate dysphagia, while 3.1% suffered from severe dysphagia. The division of SGVs was carried out in only seven patients in the study group, four of whom had no dysphagia and one only minimal dysphagia.

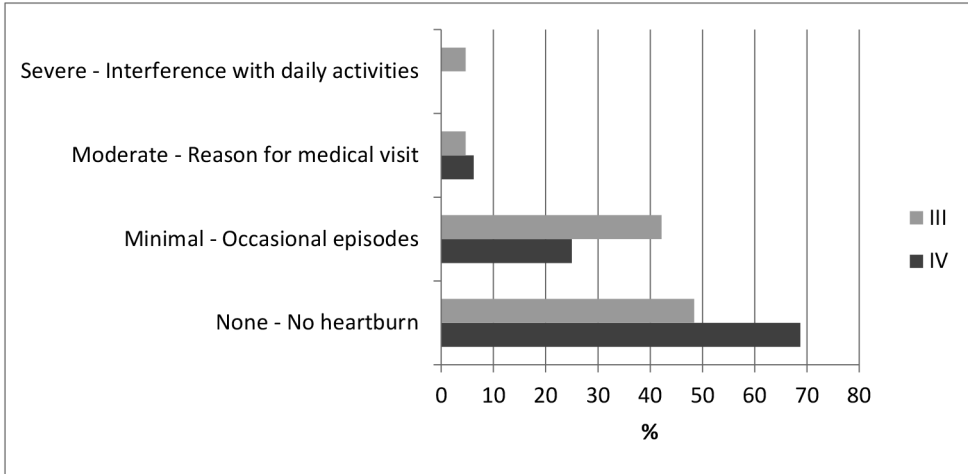


Figure 7. The heartburn rates after the long-term follow-ups

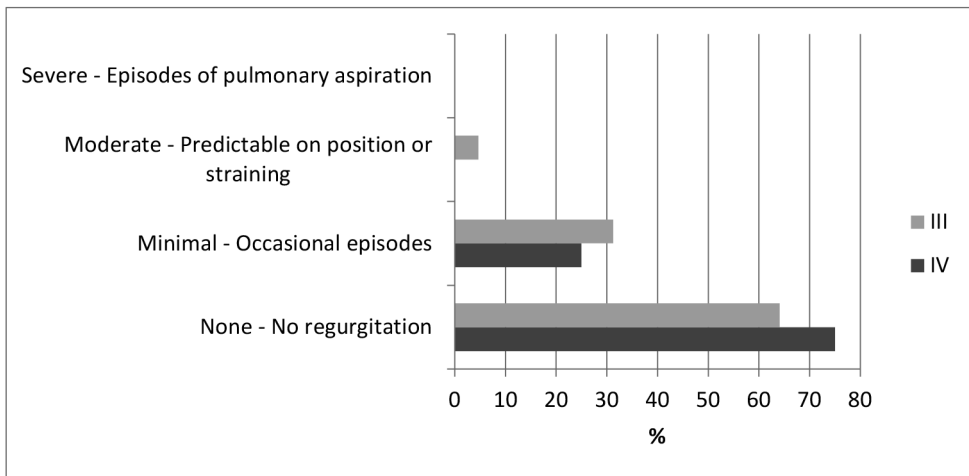


Figure 8. The regurgitation rates after the long-term follow-ups

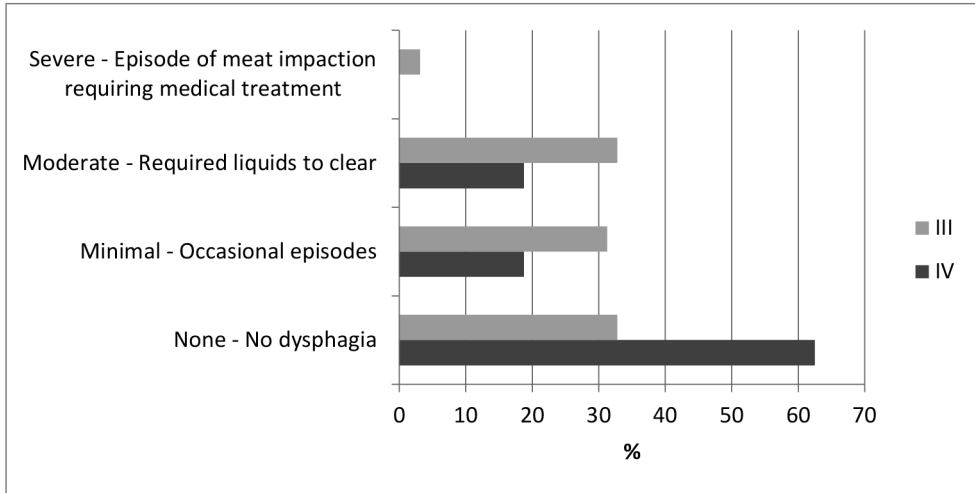


Figure 9. The dysphagia rates after the long-term follow-ups

Of the treatment-related side effects, besides dysphagia, an increase in flatulence ($p=0.024$) was observed, with 67.2% of patients reporting moderate to severe flatulence. There was no statistically significant change in bloating.

In retrospect, 89.1% of the patients would have chosen surgery as a treatment again, while 6.3% would not. The patient satisfaction increased significantly after the operation ($P<0.001$). Fifty-three (82.8%) patients were satisfied with the results of the surgery, four (6.3%) were dissatisfied, and seven (10.9%) were unsure about their opinion (Figure 10).

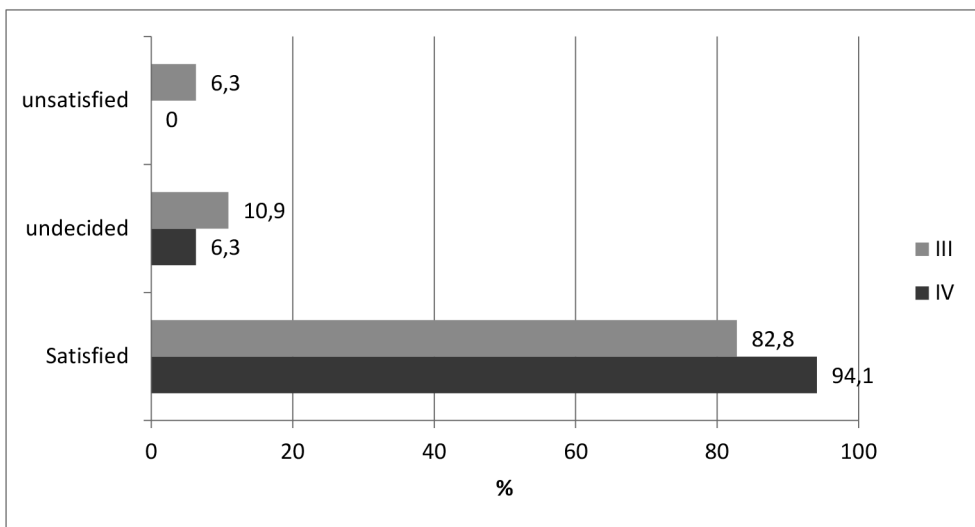


Figure 10. The satisfaction with the treatment after the long-term follow-ups

Only two patients felt the preoperative situation had been better than the postoperative situation.

7.4 Does Nissen fundoplication provide lifelong reflux control? Symptomatic outcome after 31–33 Years (IV)

In study IV, the review of the patient records revealed that the indications for the operation were ERD in 22 (57.9%) patients, positive pH or Bernstein test in 7 (18.4%) patients, and H2-blocker-resistant heartburn and/or regurgitation and a hiatus hernia or BE in 9 (23.7%) patients. The participation rate among the 24 still living patients was 70.8% (n=17), although one patient only responded to the questions concerning GSRS and satisfaction with the results of surgery. The attending patients were, on average, 43.4 (range 30–59) years old at the time of the surgery and 69.5 (range 61–87 years) years at the time of answering the questionnaires. The mean follow-up time was 32.0 (range 31.3–33.0) years. When summarizing the results of the questionnaires and the information from the hospital records, it was noted that six out of the 38 patients (15.8%) had used antireflux medication after the surgery. Two patients used occasional medication (one used PPIs and the other alginate), while four were on continuous medication (three patients used PPIs and one H2 blockers). The indications for medication were: heartburn (n=2, PPIs), upper abdominal pain (n=2, H2 blocker + alginate), and the use of non-steroidal anti-inflammatory drugs (n=2, PPIs). Endoscopy had discovered a disruption of the wrap, recurrent hiatal hernia, and esophagitis in one patient (2.6%). The patient was managed with (PPIs) and became asymptomatic. A correction of an incisional hernia had been done for one (2.6%), but neither dilatations nor reoperations were carried out. The patients experienced significantly less heartburn ($p<0.001$), regurgitation ($p<0.001$), and dysphagia ($p=0.013$) than preoperatively. The proportions of patients reporting no or only minimal heartburn, regurgitation, and dysphagia were 93.8%, 100%, and 81.3%, respectively (Figures 7–9). No patients experienced severe dysphagia. Bloating ($p=0.009$) and flatulence ($p=0.12$) were also graded as lower than preoperatively, although statistical significance was not reached in the case of flatulence. The proportions of patients reporting no or minimal bloating and flatulence were 68.8% for each symptom. Also, two patients each were undecided as regards bloating and flatulence. One patient stated the bloating was worse postoperatively, and one patient felt no difference between the pre- and postoperative states. Two patients stated the flatulence was worse postoperatively, and another two felt no difference between the pre- and postoperative states. The mean Visick score decreased from 3.94 to 0.625 ($p<0.001$), and the mean GSRS score decreased from 31.3 to 7.9 ($p<0.001$) after the follow-up. There was neither clinical nor statistical difference ($p=0.912$) between the mean 15D score of the patient group and that of the age- and sex-standardized general population (0.896 vs 0.899). The only individual dimension with a significant difference was mental function.

The scores of mental function were 0.96 for the patients and 0.86 for the general population ($p=0.008$). In retrospect, all the patients would have chosen surgery as a treatment again, and 94.1% were satisfied with the results of surgery. Only one patient was undecided about the satisfaction with the treatment because of flatulence and an inability to vomit. There were no patients rating the satisfaction level as unsatisfied (Figure 10).

8 DISCUSSION

In our studies concerning the long-term results of Nissen fundoplication before and during the laparoscopic era, we found that Nissen fundoplication may provide durable results also when applied in routine clinical practice, and in the case of successful surgery, the results may last a lifetime.

We found a similar pronounced increase in the rates of antireflux surgery after the introduction of LNF as have been reported earlier (Finks et al. 2006; Rantanen et al. 2008; Sandbu and Sundbom 2010; study I). In our material, the indications for the operation during the laparoscopic era were strict, as only patients with objectively verified GERD were operated on (study I). The study concerning ONF revealed that 76.3% of the patients had objectively verified GERD, whereas the rest were operated on due to an endoscopically verified hiatus hernia (21.1%) or BE (2.6%) and H2-blocker-resistant symptoms (study IV).

One may consider that an indication for successful elective surgery consists of three different aspects: 1) the recognition of a valid condition for a certain treatment as well as the views of 2) the surgeon and 3) the patient, and there should be no inconsistency between the three. During the 1980s and the 1990s, the primary goal in the treatment of our patient groups was to ameliorate the symptoms caused by acid reflux. The pH monitoring was carried out for 21.1% of the patients in the 1980s and for 87% of the patients in the 1990s, which probably mainly reflects the availability of the testing (study I; study IV). In the 1980s, surgeons had to rely more upon endoscopy in the preoperative testing. The views of patients have changed after the introduction of PPIs and the less-invasive laparoscopic technique. It is likely that some of the patients operated on in the 1980s might have achieved a satisfactory remission if PPIs had been available at the time, and some of the patients operated on laparoscopically in the 1990s would not have been interested in an open procedure. The views of surgeons certainly changed in the 1990s when gastrointestinal surgeons began to utilize the novel technique. In general, only a fraction of the patients with reflux-related symptoms are treated surgically (Diaz-Rubio et al. 2004; El-Serag et al. 2004; Isolauri and Laippala 1995; Ronkainen et al. 2005b), but the indications from the surgeons' perspective have varied during the last decades. Antireflux surgery has been offered as an alternative to lifelong medication, for PPI-responsive GERD, in PPI-refractory cases, as well as in severe forms of GERD (Fischella and Patti 2014; Kahrilas et al. 2008; Stefanidis et al. 2010; Zerbib et al. 2013). In our material, the patients had a long history of antireflux medication, and from the mid-1990s onwards, PPIs were by far the most common medical treatment before surgery (data not shown). Therefore, dissatisfaction with PPI treatment for one reason or another has had a major

role in choosing surgery in our long-term follow-up studies after LNF (study II; study III). One of the main reasons for the patients' unwillingness to use PPIs during the 1990s was undoubtedly the high price of the medication. As a result of the factors mentioned above, it is probable that exactly the same patients who were operated on during the 1980s would not have been operated on during the 1990s or vice versa. It can be assumed that the rise in the incidence of antireflux surgery in the 1990s after the introduction of the laparoscopic technique is explained by the surgeons offering the treatment more frequently as well as by a more willing acceptance by the patients. Therefore, it seems the introduction of the laparoscopic technique broadened the indications for fundoplication in the 1990s as the treatment became more appealing for a wider range of patients and the threshold to offer it became lower for surgeons (study I; study IV).

To some extent, the expectations on the laparoscopic procedure have proven justified, as patients are more satisfied after LNF than ONF, and a notable proportion of patients are concerned by the poor cosmetics of the incisional scar after ONF (Salminen et al. 2012). Moreover, the reoperation rate after ONF is higher because of the significant difference in postoperative incisional hernias (Broeders et al. 2009b), and the reported rates of defective wraps have been higher after ONF than LNF (Djerf et al. 2016; Luostarinen 1993; Luostarinen et al. 1993b; Rantanen et al. 1999; Salminen et al. 2012, study III; Figure 11). However, one must take into account that, in the series of Salminen et al., the ONFs

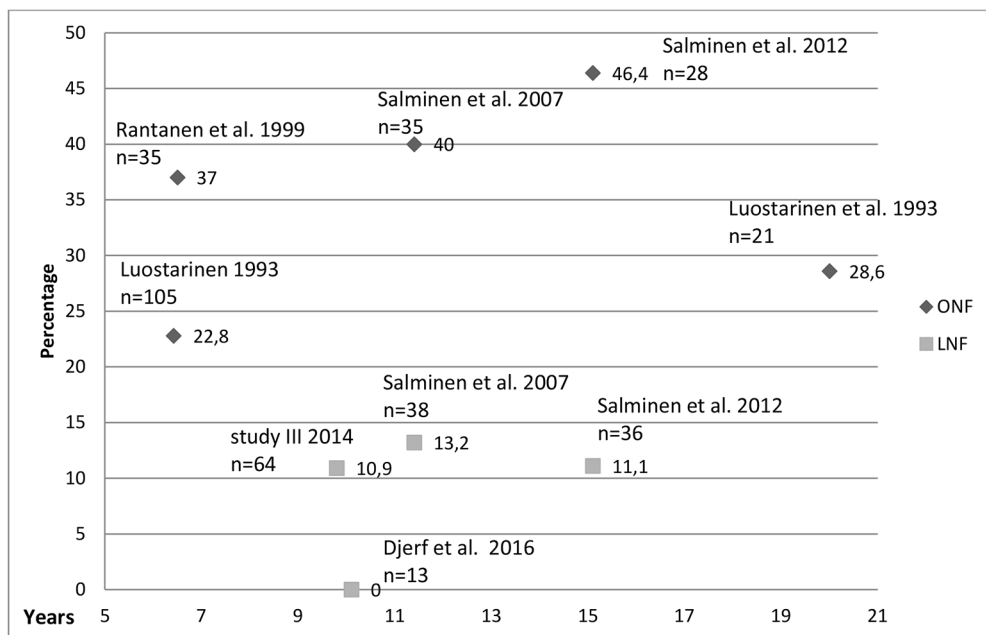


Figure 11. The percentage of endoscopically verified defective fundoplication wraps in the follow-up studies and the number of endoscopies performed (Djerf et al. 2016; Luostarinen 1993; Luostarinen et al. 1993b; Rantanen et al. 1999; Salminen et al. 2012; Salminen et al. 2007; study III).

were performed by various surgeons, while the LNFs were performed by a single specialist (Salminen et al. 2012).

In our study, 89% of the wraps were endoscopically intact ten years after LNF (study III), which compares favorably to the previous failure rates (23%-46%) reported after ONF (Luostarinen 1993; Luostarinen et al. 1993b; Rantanen et al. 1999; Salminen et al. 2012; Salminen et al. 2007). There is no obvious reason for the fact that LNF seems more durable than ONF in the long term. The operative technique varied to some extent in our material concerning the Kanta-Häme Central Hospital. The application of hiatoplasty and anchoring of the wrap expanded towards the end of the 1990s, while fibrin glue was widely used to secure the wrap during 1995-1998 (study I; Figure 6). In our data, the use of fibrin glue and hiatoplasty seemed to decrease the incidence of failure (study I; study III), and in a study by Djerf et al., hiatoplasty was also routinely used with no failed wraps (Djerf et al. 2016). In contrast to this is the fact that only sporadic hiatoplasties were performed in a study by Salminen et al. and low rate of defective wraps was still noted after LNF (11% LNF vs. 46% ONF) (Salminen et al. 2012). Although hiatoplasty was routinely utilized by some authors during the ONF era (DeMeester et al. 1986), the importance of hiatoplasty in the laparoscopic funduplications was not recognized until after the rise in the incidence of acute paraesophageal herniations after the deployment of the new technique (Hunter et al. 1999; Watson et al. 1995). During the open surgery era, wrap disruption instead of hiatal disruption/herniation was the most common problem with the durability of the wrap (Hunter et al. 1999; Stein et al. 1996). Also, in our study concerning ONF, excellent clinical results were achieved, even though hiatoplasty was not included in the operative technique (study IV). It can be contemplated that the surgical technique may vary beyond what can be described explicitly in the literature. For example, the amount and technique of dissection of the surfaces on the surgical field and the extent of mobilization may play a role in regard to the durability of the wrap, as scar formation or tendency for herniation may differ between individual techniques.

That being said, some recommendations for the operative technique can be proposed according to the current literature. A routine hiatoplasty is preferred to prevent wrap migration (DeMeester et al. 1986; Hunter et al. 1999; Watson et al. 1995). Some recommend hiatoplasty with mesh in the case of a large hiatal surface area (Frantzides et al. 2002; Oelschlager et al. 2006; Soricelli et al. 2009), but there are no long-term follow-up studies on the subject and meshes are associated with increased complication risks (Stadlhuber et al. 2009). There is some evidence to support the use of a bougie to calibrate the wrap in order to minimize postoperative dysphagia, but it seems that an experienced surgeon can achieve similar results without a bougie (Patterson et al. 2000; Somasekar et al. 2010). Very similar results can be achieved with LNF and with LTF, and with LAFs of 120° and 180°, while the LAFs seem to have slightly more limited reflux control (Broeders et al. 2013; Djerf et al. 2016; Shaw et al. 2010). LNF is associated with more extensive relief in typical GERD symptoms, while dysphagia is reported more often

than after partial funduplications (Broeders et al. 2010a; Broeders et al. 2013; Djerf et al. 2016). As the treatment-related side effects of surgical treatment favor medical treatment in milder forms of GERD, it is worth considering to pursue a maximal antireflux barrier when choosing operative treatment. LNF has been suggested for younger patients to ensure durable reflux control and LAF for older patients to minimize dysphagia (Broeders et al. 2013). However, there is no support for changing the operative technique to a new one on the basis of current literature, as none of the modifications have been proven superior. The changing of technique might predispose patients to unnecessary complications. The use of fibrin glue seems to enhance the durability of the wrap (study III), but RCTs with long-term follow-up are needed on the subject.

LNF provides powerful and durable control of acid reflux (Broeders et al. 2010a; Broeders et al. 2013; Djerf et al. 2016; Shaw et al. 2010) and is effective in suppressing the typical symptoms of GERD in the majority of patients (Broeders et al. 2009b; Djerf et al. 2016; Kellokumpu et al. 2013; Morgenthal et al. 2007b; Salminen et al. 2012; study III). We studied the longest follow-up after ONF published to date and found that, in the case of a successful fundoplication, the operation may give the patient lifelong relief of reflux symptoms (study IV).

Despite the benefits of LNF, a considerable proportion of patients are not completely satisfied, or develop treatment-related side effects and/or reinstate the antisecretory medication (Broeders et al. 2009b; Mehta et al. 2006; Morgenthal et al. 2007b; Salminen et al. 2012; Sandbu et al. 2002; Vakil et al. 2003; study II; study III). The dysphagia rates in our material concerning the Kanta-Häme Central Hospital were quite high (study III). The learning-curve effect and the instrument used to grade the symptom may have worsened the results in light of other studies. Others have reported higher rates for dilatation, even though the dysphagia rates have been lower (Morgenthal et al. 2007b). Even so, dysphagia was the most common problem among the unsatisfied patients and should not be understated (study II). To prevent dysphagia, it is important to achieve a loose wrap (DeMeester et al. 1986; Hunter et al. 1999). It seems the SGVs should be divided if a loose enough wrap is not achieved otherwise. With experience, one should consider preserving the SGVs, as the division may lead to increased bloating and the dysphagia rates have been similar in RCTs comparing the two techniques (Chrysos et al. 2001; Engstrom et al. 2011; Mardani et al. 2009; Yang et al. 2008). It may be presumed that the adverse effects and postoperatively reinstated use of medication, along with the lowered costs of conservative treatment, may have reduced the attraction of the treatment, leading to the decrease in the incidence of LNFs in the 21st century (Finks et al. 2006; Sandbu and Sundbom 2010).

The majority of the patients who are candidates for antireflux surgery are seeking improvements in their quality of life. Among the most important results in our study were the ones concerning HRQoL. We found in our long-term follow-up studies that a successful fundoplication may provide a similar HRQoL as that of the general population

(study II; study IV), but it must be taken into account that the HRQoL of the dissatisfied was reduced (study II).

There are some limitations to our studies. The participation rates in our long-term follow-up studies (study II; study III; study IV) were quite low, and the overall patient group in the ONF follow-up was relatively small (study IV). To decrease the risk of selection bias, we reviewed the patient records of the non-participating patients and checked the medical history concerning GERD. Low participation is a common problem in long-term follow-up studies. In the longest follow-up studies after ONF, the participation rates have been comparable to our study (37%-69%) (Lundell et al. 2009; Luostarinen et al. 1993b; Mardani et al. 2011; Salminen et al. 2012). Besides our study (study III), there are two others providing long-term endoscopy results after LNF. In a study by Djerf et al., 38% of the patients had undergone endoscopy in the LNF group, while Salminen et al. presented the results for a respectable 87% of patients (Djerf et al. 2016; Salminen et al. 2012). The size of our patient group (n=64) compares favorably to those of Salminen et al. (n=48) and Djerf et al. (n=13). The retrospective setting concerning subjective results is not ideal, which must be taken into account when interpreting the results. Still, one can assume the values reflect the overall satisfaction of the patients and reveal the trend of change. Despite the setting, the important factors of the operations should have been reliably detected (study I). The results of our studies concerning the Kanta-Häme Central Hospital (study I; study II; study III) do not measure the maximal efficacy of the treatment; instead, the aim was to portray a picture of the effectiveness of the treatment in routine clinical practice. The high risk of selection bias in the long-term follow-up study after ONF limits the generalization of the results as such (study IV). Rather, the results represent the subjective durability of the treatment in the case of successful Nissen fundoplication as there were no unsatisfied patients and every patient would have opted for surgery again in retrospect. The current literature and our studies do not, unfortunately, provide a comprehensive answer for how to achieve a successful Nissen fundoplication.

The strengths of our studies can be considered to include the fact that the review of the patient records and the patient interviews were carried out by independent observers (study I; study II; study III; study IV). The endoscopists did not know the results of the interview when performing the endoscopy, and the fundoplication wraps were analyzed in conjunction with the other authors from photographs (study III). The patient records (study II; study III; study IV) and the death certificates of the non-attending patients were reviewed (study IV), and the HRQoL was measured using a generic multidimensional instrument, which allowed comparisons to be made with the general population (study II; study IV). The follow-up periods were extensive in light of other studies (study II; study III; study IV).

Although excellent results have been reported in treating PPI-responsive patients (Anvari et al. 2011; Galmiche et al. 2011; Morgenthal et al. 2007a) and the rate of serious complications in Finland has been relatively low during the laparoscopic era (Rantanen et al.

2008), a prevailing practice of surgical treatment should focus on operating on the patients with failed medical treatment and an objectively verified reflux-symptom correlation (Kahrilas et al. 2008; Stefanidis et al. 2010; Zerbib et al. 2013). There is a heterogeneous group of disorders behind the symptoms of the patients with PPI failure, and the challenge is to rule out those with no reflux-symptom correlation, as no benefit from surgery is to be expected (Campos et al. 1999; Khajanchee et al. 2004; Zerbib et al. 2012), whereas, on the contrary, the patients with disturbing regurgitation or inadequate reflux control despite the medication are candidates for surgery. (Broeders et al. 2009a; del Genio et al. 2008). The currently available 60-year knowledge of fundoplication facilitates the appropriate instruction of patients about the expected outcomes and possible side effects. The surgery should be reserved for a group of carefully selected patients after they have been provided with adequate information about the benefits and harms.

9 SUMMARY AND CONCLUSIONS

This study describes the characteristics and long-term results of antireflux surgery performed in Finnish hospitals before and during the dissemination of the laparoscopic technique. The observations in this thesis support the following conclusions:

- (I) After the introduction of LNF, the surgical treatment of GERD multiplied in Kanta-Häme Central Hospital. Although only patients with objectively verified GERD were treated, the rise in the operation rates was considered to be a result of the broadening of the indications. The operative technique became more standardized towards the end of the 1990s.
- (II) Ten years after the operation, the HRQoL of the LNF cohort was close to that of the general population. Dissatisfaction with the treatment decreased the HRQoL, and dysphagia was the most common problem with the dissatisfied.
- (III) In our long-term follow-up study, the rate of intact fundoplication wraps was high, and the subjective long-term results achieved in routine clinical practice proved to be comparable to the results published from more specialized centers. For the first time, the use of fibrin glue was associated with a decreased incidence of surgical failure in the long term.
- (IV) A successful Nissen fundoplication may provide lifelong control of reflux symptoms, and the HRQoL of the patients was comparable to that of the general population over 30 years after the operation. The indications for the procedure reflected the practices of the time, and in most of the patients, GERD was verified objectively.

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11 REFERENCES

- Allison P. 1946. Peptic ulcer of the esophagus. *J Thorac Surg* 15:308–17.
- Allison P. 1951. Reflux esophagitis, sliding hiatal hernia, and the anatomy of repair. *Surg Gynecol Obstet* 92(4):419–31.
- American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. 2011b. American gastroenterological association medical position statement on the management of barrett's esophagus. *Gastroenterology* 140(3):1084–91.
- Anderson LA, Murray LJ, Murphy SJ, Fitzpatrick DA, Johnston BT, Watson RGP, McCarron P, Gavin AT. 2003. Mortality in barrett's oesophagus: Results from a population based study. *Gut* 52(8):1081–4.
- Anderson SHC, Yadegarfar G, Arastu MH, Anggiansah R, Anggiansah A. 2006. The relationship between gastro-oesophageal reflux symptoms and achalasia. *Eur J Gastroenterol Hepatol* 18(4):369–74.
- Anvari M and Allen C. 2003. Surgical outcome in gastro-esophageal reflux disease patients with inadequate response to proton pump inhibitors. *Surg Endosc* 17(7):1029–35.
- Anvari M, Allen C, Marshall J, Armstrong D, Goeree R, Ungar W, Goldsmith C. 2011. A randomized controlled trial of laparoscopic nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. *Surg Endosc* 25(8):2547–54.
- Armstrong D, Bennett JR, Blum AL, Dent J, De Dombal FT, Galmiche JP, Lundell L, Margulies M, Richter JE, Spechler SJ, et al. 1996. The endoscopic assessment of esophagitis: A progress report on observer agreement. *Gastroenterology* 111(1):85–92.
- Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. 2016. Functional esophageal disorders. *Gastroenterology* 150(6):1368–79.
- Bammer T, Hinder RA, Klaus A, Klingler PJ. 2001. Five- to eight-year outcome of the first laparoscopic nissen funduplications. *J Gastrointest Surg* 5(1):42–8.
- Barrett N. 1950. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg* 38(150):175–82.
- Barrett N. 1954. Hiatus hernia: A review of some controversial points. *Br J Surg* 42(173):231–43.
- Bello B, Zoccali M, Gullo R, Allaix ME, Herbella FA, Gasparaitis A, Patti MG. 2013. Gastroesophageal reflux disease and antireflux surgery-what is the proper preoperative work-up?. *J Gastrointest Surg* 17(1).
- Bennett C, Moayyedi P, Corley DA, DeCaestecker J, Falck-Ytter Y, Falk G, Vakil N, Sanders S, Vieth M, Inadomi J, et al. 2015. BOB CAT: A large-scale review and delphi consensus for management of barrett's esophagus with no dysplasia, indefinite for, or low-grade dysplasia. *Am J Gastroenterol* 110(5):662–82.
- Bowditch H. 1853. A treatise on diaphragmatic hernia. Buffalo: Jewett, Thomas & co.
- Braghetto I, Korn O, Csendes A, Valladares H, Davanzo C, Debandi A. 2012. Radiologic and endoscopic characteristics of laparoscopic antireflux wrap: Correlation with outcome. *Int Surg* 97(3):189–97.

- Bredenoord AJ, Weusten BLAM, Smout AJPM. 2005. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. *Gut* 54(12):1810–7.
- Bredenoord AJ, Weusten BLAM, Timmer R, Conchillo JM, Smout AJPM. 2006. Addition of esophageal impedance monitoring to pH monitoring increases the yield of symptom association analysis in patients off PPI therapy. *Am J Gastroenterol* 101(3):453–9.
- Bredenoord AJ, Fox M, Kahrilas PJ, Pandolfino JE, Schwizer W, Smout AJPM, International High Resolution Manometry Working Group. 2012. Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography. *Neurogastroenterol Motil* 24(Suppl 1):57–65.
- Broeders JA, Draaisma WA, Bredenoord AJ, de Vries DR, Rijnhart-de Jong HG, Smout AJ, Gooszen HG. 2009a. Oesophageal acid hypersensitivity is not a contraindication to nissen fundoplication. *Br J Surg* 96(9):1023–30.
- Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. 2009b. Ten-year outcome of laparoscopic and conventional nissen fundoplication: Randomized clinical trial. *Ann Surg* 250(5):698–706.
- Broeders JAJL, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, Smout AJPM, Broeders IAMJ, Hazebroek EJ. 2010a. Systematic review and meta-analysis of laparoscopic nissen (posterior total) versus toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 97(9):1318–30.
- Broeders JA, Draaisma WA, Bredenoord AJ, Smout AJ, Broeders IA, Gooszen HG. 2010b. Long-term outcome of nissen fundoplication in non-erosive and erosive gastro-oesophageal reflux disease. *Br J Surg* 97(6):845–52.
- Broeders JAJL, Bredenoord AJ, Hazebroek EJ, Broeders IAMJ, Gooszen HG, Smout AJPM. 2011a. Effects of anti-reflux surgery on weakly acidic reflux and belching. *Gut* 60(4):435–41.
- Broeders JA, Sportel IG, Jamieson GG, Nijjar RS, Granchi N, Myers JC, Thompson SK. 2011b. Impact of ineffective oesophageal motility and wrap type on dysphagia after laparoscopic fundoplication. *Br J Surg* 98(10):1414–21.
- Broeders JAJL, Draaisma WA, Rijnhart-de Jong HG, Smout AJPM, van Lanschot JJB, Broeders IAMJ, Gooszen HG. 2011c. Impact of surgeon experience on 5-year outcome of laparoscopic nissen fundoplication. *Arch Surg* 146(3):340–6.
- Broeders JA, Broeders EA, Watson DI, Devitt PG, Holloway RH, Jamieson GG. 2013. Objective outcomes 14 years after laparoscopic anterior 180-degree partial versus nissen fundoplication: Results from a randomized trial. *Ann Surg* 258(2):233–9.
- Bytzer P, Jones R, Vakil N, Junghard O, Lind T, Wernersson B, Dent J. 2012. Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 10(12):1360–6.
- Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA. 1990. Prevalence of columnar-lined (barrett's) esophagus. comparison of population-based clinical and autopsy findings. *Gastroenterology* 99(4):918–22.
- Campos GM, Peters JH, DeMeester TR, Oberg S, Crookes PF, Tan S, DeMeester SR, Hagen JA, Bremner CG. 1999. Multivariate analysis of factors predicting outcome after laparoscopic nissen fundoplication. *J Gastrointest Surg* 3(3):292–300.
- Carbo AI, Kim RH, Gates T, D'Agostino HR. 2014. Imaging findings of successful and failed fundoplication. *Radiographics* 34(7):1873–84.
- Centers for Disease Control and Prevention. 2002. Measuring healthy days. Atlanta, Georgia: CDC.

- Chandrasoma PT, Der R, Dalton P, Kobayashi G, Ma Y, Peters J, Demeester T. 2001. Distribution and significance of epithelial types in columnar-lined esophagus. *Am J Surg Pathol* 25(9):1188–93.
- Chandrasoma P, Wijetunge S, DeMeester S, Ma Y, Hagen J, Zambis L, DeMeester T. 2012. Columnar-lined esophagus without intestinal metaplasia has no proven risk of adenocarcinoma. *Am J Surg Pathol* 36(1):1–7.
- Chang EY, Morris CD, Seltman AK, O'Rourke RW, Chan BK, Hunter JG, Jobe BA. 2007. The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: A systematic review. *Ann Surg* 246(1):11–21.
- Chassany O, Holtmann G, Malagelada J, Gebauer U, Doerfler H, Devault K. 2008. Systematic review: Health-related quality of life (HRQoL) questionnaires in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 27(11):1053–70.
- Chey WD, Mody RR, Izat E. 2010. Patient and physician satisfaction with proton pump inhibitors (PPIs): Are there opportunities for improvement?. *Dig Dis Sci* 55(12):3415–22.
- Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. 1997. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis. *Gastroenterology* 112(6):1798–810.
- Chrysos E, Tzortzinis A, Tsiaoussis J, Athanasakis H, Vassilakis J, Xynos E. 2001. Prospective randomized trial comparing nissen to nissen-rossetti technique for laparoscopic fundoplication. *Am J Surg* 182(3):215–21.
- Coleman HG, Bhat S, Murray LJ, McManus D, Gavin AT, Johnston BT. 2011. Increasing incidence of barrett's oesophagus: A population-based study. *Eur J Epidemiol* 26(9):739–45.
- Collis J. 1957. An operation for hiatus hernia with short esophagus. *J Thorac Surg* 34(6):768–73.
- Cook MB, Wild CP, Everett SM, Hardie LJ, Bani-Hani KE, Martin IG, Forman D. 2007. Risk of mortality and cancer incidence in barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 16(10):2090–6.
- Cook MB, Chow W, Devesa SS. 2009. Oesophageal cancer incidence in the united states by race, sex, and histologic type, 1977–2005. *Br J Cancer* 101(5):855–9.
- Csendes A, Braghetto I, Burdiles P, Smok G, Henriquez A, Burgos AM. 2009. Late results of the surgical treatment of 125 patients with short-segment barrett esophagus. *Arch Surg* 144(10):921–7.
- Cundy T and Mackay J. 2011. Proton pump inhibitors and severe hypomagnesaemia. *Curr Opin Gastroenterol* 27(2):180–5.
- Dallemagne BMD, Weerts JMMD, Jehaes CMD, Markiewicz SMD, Lombard RMD. 1991. Laparoscopic nissen fundoplication: Preliminary report. *Surg Laparosc Endosc* 1(3):138–43.
- de Bortoli N, Martinucci I, Bertani L, Russo S, Franchi R, Furnari M, Tolone S, Bordini G, Bolognesi V, Bellini M, et al. 2016. Esophageal testing: What we have so far. *World J Gastrointest Pathophysiol* 7(1):72–85.
- del Genio G, Tolone S, del Genio F, Aggarwal R, d'Alessandro A, Allaria A, Rossetti G, Bruscianno L, del Genio A. 2008. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. *J Gastrointest Surg* 12(9):1491–6.
- DeMeester SR. 2015. Barrett's oesophagus: Treatment with surgery. *Best Pract Res Clin Gastroenterol* 29(1):211–7.
- Demeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW, Skinner DB. 1976. Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 184(4):459–70.

- DeMeester TR, Bonavina L, Albertucci M. 1986. Nissen fundoplication for gastroesophageal reflux disease. evaluation of primary repair in 100 consecutive patients. *Ann Surg* 204(1):9–20.
- Dent J, Vakil N, Jones R, Bytzer P, Schoning U, Halling K, Junghard O, Lind T. 2010. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: The diamond study. *Gut* 59(6):714–21.
- Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, Locke GR3, Rodriguez-Artalejo F. 2004. Symptoms of gastro-oesophageal reflux: Prevalence, severity, duration and associated factors in a spanish population. *Aliment Pharmacol Ther* 19(1):95–105.
- Djerf P, Montgomery A, Hallerback B, Hakansson H, Johnsson F. 2016. One- and ten-year outcome of laparoscopic anterior 120degree versus total fundoplication: A double-blind, randomized multicenter study. *Surg Endosc* 30(1):168–77.
- Doi T, Ichikawa S, Miyano G, Lane GJ, Miyahara K, Yamataka A. 2008. A new technique for preventing wrap disruption/migration after laparoscopic nissen fundoplication: An experimental study. *J Laparoendosc Adv Surg Tech A* 18(1):179–82.
- Donahue PE, Larson GM, Stewardson RH, Bombeck CT. 1977. Floppy nissen fundoplication. *Rev Surg* 34(4):223–4.
- Dor J, Humbert P, Dor V, Figarella J. 1962. L'intérêt de la technique de nissen modifiée dans la prévention du reflux après cardiomyotomie extramuqueuse de heller. *Memoires. Academie De Chirurgie* 27:877–82.
- Elhak NG, Mostafa M, Salah T, Haleem M. 2008. Duodenogastroesophageal reflux: Results of medical treatment and antireflux surgery. *Hepatogastroenterology* 55(81):120–6.
- Eloubeidi MA, Mason AC, Desmond RA, El-Serag HB. 2003. Temporal trends (1973–1997) in survival of patients with esophageal adenocarcinoma in the united states: A glimmer of hope?. *Am J Gastroenterol* 98(7):1627–33.
- El-Serag HB, Petersen NJ, Carter J, Graham DY, Richardson P, Genta RM, Rabeneck L. 2004. Gastroesophageal reflux among different racial groups in the united states. *Gastroenterology* 126(7):1692–9.
- Engstrom C, Blomqvist A, Dalenback J, Lonroth H, Ruth M, Lundell L. 2004. Mechanical consequences of short gastric vessel division at the time of laparoscopic total fundoplication. *J Gastrointest Surg* 8(4):442–7.
- Engstrom C, Jamieson GG, Devitt PG, Watson DI. 2011. Meta-analysis of two randomized controlled trials to identify long-term symptoms after division of the short gastric vessels during nissen fundoplication. *Br J Surg* 98(8):1063–7.
- Erichsen R, Horvath-Puho E, Lund JL, Dellon ES, Shaheen NJ, Pedersen L, Davey Smith G, Sorensen HT. 2017. Mortality and cardiovascular diseases risk in patients with barrett's oesophagus: A population-based nationwide cohort study. *Aliment Pharmacol Ther* 45(7):973–82.
- Fei L, Rossetti G, Moccia F, Marra T, Guadagno P, Docimo L, Cimmino M, Napolitano V, Docimo G, Napoletano D, et al. 2013. Is the advanced age a contraindication to GERD laparoscopic surgery? results of a long term follow-up. *BMC Surgery* 13(Suppl 2):S13.
- Finks JF, Wei Y, Birkmeyer JD. 2006. The rise and fall of antireflux surgery in the united states. *Surg Endosc* 20(11):1698–701.
- Fisichella PM and Patti MG. 2014. GERD procedures: When and what? *J Gastrointest Surg* 18(11):2047–53.
- Fitzgerald RC, di Pietro M, Ragunath K, Ang Y, Kang J, Watson P, Trudgill N, Patel P, Kaye PV, Sanders S, et al. 2014. British society of gastroenterology guidelines on the diagnosis and management of barrett's oesophagus. *Gut* 63(1):7–42.

- Fohl AL and Regal RE. 2011. Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all?. *World J Gastrointest Pharmacol Ther* 2(3):17–26.
- Frantzides CT, Madan AK, Carlson MA, Stavropoulos GP. 2002. A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair vs simple cruroplasty for large hiatal hernia. *Arch Surg* 137(6):649–52.
- Freedberg DE, Kim LS, Yang Y. 2017. The risks and benefits of long-term use of proton pump inhibitors: Expert review and best practice advice from the american gastroenterological association. *Gastroenterology* 152(4):706–15.
- Fuchs KH, DeMeester TR, Albertucci M. 1987. Specificity and sensitivity of objective diagnosis of gastroesophageal reflux disease. *Surgery* 102(4):575–80.
- Funch-Jensen P, Bendixen A, Iversen MG, Kehlet H. 2008. Complications and frequency of redo antireflux surgery in denmark: A nationwide study, 1997–2005. *Surg Endosc* 22(3):627–30.
- Galmiche J, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, Langstrom G, Lind T, Lundell L, LOTUS Trial Collaborators. 2011. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: The LOTUS randomized clinical trial. *JAMA* 305(19):1969–77.
- Galvani C, Fisichella PM, Gorodner MV, Perretta S, Patti MG. 2003. Symptoms are a poor indicator of reflux status after fundoplication for gastroesophageal reflux disease: Role of esophageal functions tests. *Arch Surg* 138(5):514–8.
- Garg SK and Gurusamy KS. 2015. Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. *Cochrane Database of Systematic Reviews* 11:003243.
- Gasiorowska A, Poh CH, Fass R. 2009. Gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS) – is it one disease or an overlap of two disorders? *Dig Dis Sci* 54(9):1829–34.
- Gholoum S, Feldman LS, Andrew CG, Bergman S, Demyttenaere S, Mayrand S, Stanbridge DD, Fried GM. 2006. Relationship between subjective and objective outcome measures after heller myotomy and dor fundoplication for achalasia. *Surg Endosc* 20(2):214–9.
- Granderath FA, Schweiger UM, Kamolz T, Asche KU, Pointner R. 2005. Laparoscopic nissen fundoplication with prosthetic hiatal closure reduces postoperative intrathoracic wrap herniation: Preliminary results of a prospective randomized functional and clinical study. *Arch Surg* 140(1):40–8.
- Grotenhuis BA, Wijnhoven BPL, Bessell JR, Watson DI. 2008. Laparoscopic antireflux surgery in the elderly. *Surg Endosc* 22(8):1807–12.
- Gyawali CP, Bredenoord AJ, Conklin JL, Fox M, Pandolfino JE, Peters JH, Roman S, Staiano A, Vaezi MF. 2013. Evaluation of esophageal motor function in clinical practice. *Neurogastroenterol Motil* 25(2):99–133.
- Hahn HP, Blount PL, Ayub K, Das KM, Souza R, Spechler S, Odze RD. 2009. Intestinal differentiation in metaplastic, nongoblet columnar epithelium in the esophagus. *Am J Surg Pathol* 33(7):1006–15.
- Hallerback B, Unge P, Carling L, Edwin B, Glise H, Havu N, Lyrenas E, Lundberg K. 1994. Omeprazole or ranitidine in long-term treatment of reflux esophagitis. the scandinavian clinics for united research group. *Gastroenterology* 107(5):1305–11.
- Han MS and Peters JH. 2014. Ambulatory esophageal pH monitoring. *Gastrointest Endosc Clin N Am* 24(4):581–94.

- Hiebert C and Belsey R. 1961. Incompetency of the gastric cardia without radiologic evidence of hiatal hernia. the diagnosis and management of 71 cases. *J Thorac Cardiovasc Surg* 42:352–62.
- Hill LD, Kozarek RA, Kraemer SJ, Aye RW, Mercer CD, Low DE, Pope CE2. 1996. The gastroesophageal flap valve: In vitro and in vivo observations. *Gastrointest Endosc* 44(5):541–7.
- Hill LDMD. 1967. An effective operation for hiatal hernia: An eight year appraisal. *Ann Surg* 166(4):681–92.
- Horgan S, Pohl D, Bogetti D, Eubanks T, Pellegrini C. 1999. Failed antireflux surgery: What have we learned from reoperations?. *Arch Surg* 134(8):809–15.
- Hungin AP, Rubin G, O’Flanagan H. 1999. Factors influencing compliance in long-term proton pump inhibitor therapy in general practice. *Br J Gen Pract* 49(443):463–4.
- Hunter JG, Smith CD, Branum GD, Waring JP, Trus TL, Cornwell M, Galloway K. 1999. Laparoscopic fundoplication failures: Patterns of failure and response to fundoplication revision. *Ann Surg* 230(4):595–604.
- Hvid-Jensen F, Pedersen L, Munk EM, Drewes AM, Funch-Jensen P. 2011a. Long-term complications to reflux disease in community practice. A 17-year cohort study of 4706 patients. *Scand J Gastroenterol* 46(10):1179–86.
- Hvid-Jensen F, Pedersen L, Drewes AM, Sorensen HT, Funch-Jensen P. 2011b. Incidence of adenocarcinoma among patients with barrett’s esophagus. *N Engl J Med* 365(15):1375–83.
- Ielpo B, Martin P, Vazquez R, Corripio R, San Roman J, Acedo F, La Puente F, Torres A, Gravante G, Fernandez-Nespral V. 2011. Long-term results of laparoscopic nissen fundoplication with or without short gastric vessels division. *Surg Laparosc Endosc Percutan Tech* 21(4):267–70.
- Isolauri J and Laippala P. 1995. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. *Ann Med* 27(1):67–70.
- Isolauri J, Viljakka M, Helin H, Lehto MU, Luostarinen M. 1997a. Disruption of experimental fundic folds is prevented by interserosal scarring. *Br J Surg* 84(4):548–50.
- Isolauri J, Luostarinen M, Isolauri E, Reinikainen P, Viljakka M, Keyrilainen O. 1997b. Natural course of gastroesophageal reflux disease: 17–22 year follow-up of 60 patients. *Am J Gastroenterol* 92(1):37–41.
- Jailwala J, Massey B, Staff D, Shaker R, Hogan W. 2001. Post-fundoplication symptoms: The role for endoscopic assessment of fundoplication integrity. *Gastrointest Endosc* 54(3):351–6.
- Jobe BA, Kahrilas PJ, Vernon AH, Sandone C, Gopal DV, Swanstrom LL, Aye RW, Hill LD, Hunter JG. 2004. Endoscopic appraisal of the gastroesophageal valve after antireflux surgery. *Am J Gastroenterol* 99(2):233–43.
- Johnsson F, Joelsson B, Isberg PE. 1987. Ambulatory 24 hour intraesophageal pH-monitoring in the diagnosis of gastroesophageal reflux disease. *Gut* 28(9):1145–50.
- Jung H, Halder S, McNally M, Locke GR3, Schleck CD, Zinsmeister AR, Talley NJ. 2007. Overlap of gastro-oesophageal reflux disease and irritable bowel syndrome: Prevalence and risk factors in the general population. *Aliment Pharmacol Ther* 26(3):453–61.
- Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. 1986. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 91(4):897–904.
- Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, Johnson SP, Allen J, Brill JV, American Gastroenterological Association. 2008. American gastroenterological association medical position statement on the management of gastroesophageal reflux disease. *Gastroenterology* 135(4):1383–91.

- Kahrilas PJ, Howden CW, Hughes N. 2011. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. *Am J Gastroenterol* 106(8):1419–25.
- Kamolz T, Granderath FA, Schweiger UM, Pointner R. 2005. Laparoscopic nissen fundoplication in patients with nonerosive reflux disease. long-term quality-of-life assessment and surgical outcome. *Surg Endosc* 19(4):494–500.
- Katzka DA. 2014. The role of barium esophagography in an endoscopy world. *Gastrointest Endosc Clin N Am* 24(4):563–80.
- Kauttu TME, Rantanen TK, Sihvo EI, Rasanen JV, Puolakkainen P, Salo JA. 2011. Esophageal adenocarcinoma arising after antireflux surgery: A population-based analysis. *Eur J Cardiothorac Surg* 40(6):1450–4.
- Kellokumpu I, Voutilainen M, Haglund C, Farkkila M, Roberts PJ, Kautiainen H. 2013. Quality of life following laparoscopic nissen fundoplication: Assessing short-term and long-term outcomes. *World J Gastroenterol* 19(24):3810–8.
- Khajanchee YS, O'Rourke RW, Lockhart B, Patterson EJ, Hansen PD, Swanstrom LL. 2002. Postoperative symptoms and failure after antireflux surgery. *Arch Surg* 137(9):1008–13.
- Khajanchee YS, Hong D, Hansen PD, Swanstrom LL. 2004. Outcomes of antireflux surgery in patients with normal preoperative 24-hour pH test results. *Am J Surg* 187(5):599–603.
- Khajanchee YS, Dunst CM, Swanstrom LL. 2009. Outcomes of nissen fundoplication in patients with gastroesophageal reflux disease and delayed gastric emptying. *Arch Surg* 144(9):823–8.
- Klaus A, Hinder RA, DeVault KR, Achem SR. 2003. Bowel dysfunction after laparoscopic antireflux surgery: Incidence, severity, and clinical course. *Am J Med* 114(1):6–9.
- Kline MM, Ewing M, Simpson N, Laine L. 2008. The utility of intraluminal impedance in patients with gastroesophageal reflux disease-like symptoms but normal endoscopy and 24-hour pH testing. *Clin Gastroenterol Hepatol* 6(8):880–5.
- Koch OO, Asche KU, Berger J, Weber E, Granderath FA, Pointner R. 2011. Influence of the size of the hiatus on the rate of reherniation after laparoscopic fundoplication and refundoplication with mesh hiatoplasty. *Surg Endosc* 25(4):1024–30.
- Koch OO, Spaun G, Antoniou SA, Rabl C, Kohler G, Emmanuel K, Ofner D, Pointner R. 2013. Endoscopic grading of the gastroesophageal flap valve is correlated with reflux activity and can predict the size of the esophageal hiatus in patients with gastroesophageal reflux disease. *Surg Endosc* 27(12):4590–5.
- Koetje JH, Nieuwenhuijs VB, Irvine T, Mayne GC, Watson DI. 2016. Measuring outcomes of laparoscopic anti-reflux surgery: Quality of life versus symptom scores?. *World J Surg* 40(5):1137–44.
- Kornmo TS and Ruud TE. 2008. Long-term results of laparoscopic nissen fundoplication due to gastroesophageal reflux disease. A ten year follow-up in a low volume center. *Scand J Surg* 97(3):227–30.
- Koskinen S, Lundqvist A, Ristiluoma N. 2012. Health, functional capacity and welfare in finland in 2011. Helsinki: National Institute for Health and Welfare (THL). Report nr 68/2012.
- Kulinna-Cosentini C, Schima W, Ba-Ssalamah A, Cosentini EP. 2014. MRI patterns of nissen fundoplication: Normal appearance and mechanisms of failure. *Eur Radiol* 24(9):2137–45.
- Kunio NR, Dolan JP, Hunter JG. 2015. Short esophagus. *Surg Clin North Am* 95(3):641–52.
- Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. 2012. Risk of clostridium difficile infection with acid suppressing drugs and antibiotics: Meta-analysis. *Am J Gastroenterol* 107(7):1011–9.

- Lacy BE, Talley NJ, Locke GR3, Bouras EP, DiBaise JK, El-Serag HB, Abraham BP, Howden CW, Moayyedi P, Prather C. 2012. Review article: Current treatment options and management of functional dyspepsia. *Aliment Pharmacol Ther* 36(1):3–15.
- Lagergren J, Bergstrom R, Lindgren A, Nyren O. 1999. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 340(11):825–31.
- Lamb PJ, Myers JC, Jamieson GG, Thompson SK, Devitt PG, Watson DI. 2009. Long-term outcomes of revisional surgery following laparoscopic fundoplication. *Br J Surg* 96(4):391–7.
- Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. 2008. Continuing rapid increase in esophageal adenocarcinoma in england and wales. *Am J Gastroenterol* 103(11):2694–9.
- Lima M, Domini M, Libri M, Garzi A. 1997. Laparoscopic nissen fundoplication with fibrin glue: Experimental study on pigs. *Eur J Pediatr Surg* 7(1):4–7.
- Lind T, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, Junghard O, Lauritsen K, Lundell L, Pedersen SA, et al. 1997. Heartburn without oesophagitis: Efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 32(10):974–9.
- Lindeboom MYA, Ringers J, van Rijn PJJ, Neijenhuis P, Stokkel MPM, Masclee AAM. 2004. Gastric emptying and vagus nerve function after laparoscopic partial fundoplication. *Ann Surg* 240(5):785–90.
- Lo W and Mashimo H. 2015. Critical assessment of endoscopic techniques for gastroesophageal reflux disease. *J Clin Gastroenterol* 49(9):720–4.
- Lodrup A, Pottgard A, Hallas J, Bytzer P. 2014. Use of proton pump inhibitors after antireflux surgery: A nationwide register-based follow-up study. *Gut* 63(10):1544–9.
- Lord RVN, Kaminski A, Oberg S, Bowrey DJ, Hagen JA, DeMeester SR, Sillin LF, Peters JH, Crookes PF, DeMeester TR. 2002. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after nissen fundoplication. *J Gastrointest Surg* 6(1):3–9.
- Lowham AS, Filipi CJ, Hinder RA, Swanstrom LL, Stalter K, dePaula A, Hunter JG, Buglewicz TG, Haake K. 1996. Mechanisms and avoidance of esophageal perforation by anesthesia personnel during laparoscopic foregut surgery. *Surg Endosc* 10(10):979–82.
- Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, et al. 1999. Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the los angeles classification. *Gut* 45(2):172–80.
- Lundell L, Miettinen P, Myrvold HE, Hatlebakk JG, Wallin L, Engstrom C, Julkunen R, Montgomery M, Malm A, Lind T, et al. 2009. Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clin Gastroenterol Hepatol* 7(12):1292–8.
- Lundell L. 2014. Borderline indications and selection of gastroesophageal reflux disease patients: ‘Is surgery better than medical therapy?’ *Dig Dis* 32(1–2):152–5.
- Luostarinen M. 1993. Nissen fundoplication for reflux esophagitis. long-term clinical and endoscopic results in 109 of 127 consecutive patients. *Ann Surg* 217(4):329–37.
- Luostarinen ME, Isolauri JO, Koskinen MO, Laitinen JO, Matikainen MJ, Lindholm TS. 1993a. Refundoplication for recurrent gastroesophageal reflux. *World J Surg* 17(5):587–93.
- Luostarinen M, Isolauri J, Laitinen J, Koskinen M, Keyrilainen O, Markkula H, Lehtinen E, Uusitalo A. 1993b. Fate of nissen fundoplication after 20 years. A clinical, endoscopic, and functional analysis. *Gut* 34(8):1015–20.

- Luostarinen ME and Isolauri JO. 1999a. Randomized trial to study the effect of fundic mobilization on long-term results of nissen fundoplication. *Br J Surg* 86(5):614–8.
- Luostarinen ME and Isolauri JO. 1999b. Surgical experience improves the long-term results of nissen fundoplication. *Scand J Gastroenterol* 34(2):117–20.
- Luostarinen M, Virtanen J, Koskinen M, Matikainen M, Isolauri J. 2001. Dysphagia and oesophageal clearance after laparoscopic versus open nissen fundoplication. A randomized, prospective trial. *Scand J Gastroenterol* 36(6):565–71.
- Malferteiner P, Lind T, Willich S, Vieth M, Jaspersen D, Labenz J, Meyer-Sabellek W, Junghard O, Stolte M. 2005. Prognostic influence of barrett's oesophagus and helicobacter pylori infection on healing of erosive gastro-oesophageal reflux disease (GORD) and symptom resolution in non-erosive GORD: Report from the ProGORD study. *Gut* 54(6):746–51.
- Mardani J, Lundell L, Lonroth H, Dalenback J, Engstrom C. 2009. Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. *Br J Surg* 96(1):61–5.
- Mardani J, Lundell L, Engstrom C. 2011. Total or posterior partial fundoplication in the treatment of GERD: Results of a randomized trial after 2 decades of follow-up. *Ann Surg* 253(5):875–8.
- Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. 2003. Non-erosive reflux disease (NERD)-acid reflux and symptom patterns. *Aliment Pharmacol Ther* 17(4):537–45.
- Matikainen M. 1984. Antrectomy, roux-en-Y reconstruction and vagotomy for recurrent reflux oesophagitis. *Acta Chir Scand* 150(8):643–5.
- Mehta S, Bennett J, Mahon D, Rhodes M. 2006. Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: Seven-year follow-up. *J Gastrointest Surg* 10(9):1312–6.
- Memon MA, Subramanya MS, Hossain MB, Yunus RM, Khan S, Memon B. 2015. Laparoscopic anterior versus posterior fundoplication for gastro-esophageal reflux disease: A meta-analysis and systematic review. *World J Surg* 39(4):981–96.
- Migaczewski M, Zub-Pokrowiecka A, Grzesiak-Kuik A, Pedziwiatr M, Major P, Rubinkiewicz M, Winiarski M, Natkaniec M, Budzynski A. 2015. Incidence of true short esophagus among patients submitted to laparoscopic nissen fundoplication. *Wideochir Inne Tech Mao Inwazyjne* 10(1):10–4.
- Mittal SK, Awad ZT, Tasset M, Filipi CJ, Dickason TJ, Shinno Y, Marsh RE, Tomonaga TJ, Lerner C. 2000. The preoperative predictability of the short esophagus in patients with stricture or paraesophageal hernia. *Surg Endosc* 14(5):464–8.
- Moayyedi P, Yuan Y, Leontiadis G, CAG Clinical Affairs. 2013. Canadian association of gastroenterology position statement: Hip fracture and proton pump inhibitor therapy-a 2013 update. *Can J Gastroenterol* 27(10):593–5.
- Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. 2007a. Who will fail laparoscopic nissen fundoplication? preoperative prediction of long-term outcomes. *Surg Endosc* 21(11):1978–84.
- Morgenthal CB, Shane MD, Stival A, Gletsu N, Milam G, Swafford V, Hunter JG, Smith CD. 2007b. The durability of laparoscopic nissen fundoplication: 11-year outcomes. *J Gastrointest Surg* 11(6):693–700.
- Nadaletto BF, Herbella FAM, Patti MG. 2016. Gastroesophageal reflux disease in the obese: Pathophysiology and treatment. *Surgery* 159(2):475–86.

- Nasseri-Moghaddam S, Razjouyan H, Nouraei M, Alimohammadi M, Mamarabadi M, Vahedi H, Pourshams A, Mohamadnejad M, Zamani F, Sadr F, et al. 2007. Inter- and intra-observer variability of the los angeles classification: A reassessment. *Arch Iran Med* 10(1):48–53.
- Negre JB. 1983. Post-fundoplication symptoms. do they restrict the success of nissen fundoplication?. *Ann Surg* 198(6):698–700.
- Ng A, Yong D, Hazebroek E, Berry H, Radajewski R, Leibman S, Smith GS. 2009. Omission of the calibration bougie in laparoscopic repair of paraesophageal hernia. *Surg Endosc* 23(11):2505–8.
- Nissen R. 1937. Die transpleurale resection der kardia. *Deutsche Zeitschrift Für Chirurgie* 249:311–6.
- Nissen R. 1956a. Eine einfache operation zur beeinflussung der refluxoesophagitis. *Schweizerische Medizinische Wochenschrift* 86:590–2.
- Nissen R. 1956b. Gastropexy as the lone procedure in the surgical repair of hiatus hernia. *Am J Surg* 92(3):389–92.
- Nissen R. 1981. In: Fundoplication und gastropexie bei refluxkrankheit und hiatushernie. Nissen R, Rossetti M, Siewert R, editors. Stuttgart: Thieme verlag.
- Odze RD. 2011. What the gastroenterologist needs to know about the histology of barrett's esophagus. *Curr Opin Gastroenterol* 27(4):389–96.
- Oelschlager BK, Barreca M, Chang L, Oleynikov D, Pellegrini CA. 2003. Clinical and pathologic response of barrett's esophagus to laparoscopic antireflux surgery. *Ann Surg* 238(4):458–64.
- Oelschlager BK, Pellegrini CA, Hunter J, Soper N, Brunt M, Sheppard B, Jobe B, Polissar N, Mitsumori L, Nelson J, et al. 2006. Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair: A multicenter, prospective, randomized trial. *Ann Surg* 244(4):481–90.
- O'Hanrahan T, Marples M, Bancewicz J. 1990. Recurrent reflux and wrap disruption after nissen fundoplication: Detection, incidence and timing. *Br J Surg* 77(5):545–7.
- Orringer MB and Sloan H. 1978. Combined collis-nissen reconstruction of the esophagogastric junction. *Ann Thorac Surg* 25(1):16–21.
- Palmer ED. 1968. The hiatus hernia-esophagitis-esophageal stricture complex. twenty-year prospective study. *Am J Med* 44(4):566–79.
- Pandolfino JE and Krishnan K. 2014. Do endoscopic antireflux procedures fit in the current treatment paradigm of gastroesophageal reflux disease? *Clin Gastroenterol Hepatol* 12(4):544–54.
- Parrilla P, Martinez de Haro LF, Ortiz A, Munitiz V, Molina J, Bermejo J, Canteras M. 2003. Long-term results of a randomized prospective study comparing medical and surgical treatment of barrett's esophagus. *Ann Surg* 237(3):291–8.
- Patterson EJ, Herron DM, Hansen PD, Ramzi N, Standage BA, Swanstrom LL. 2000. Effect of an esophageal bougie on the incidence of dysphagia following nissen fundoplication: A prospective, blinded, randomized clinical trial. *Arch Surg* 135(9):1055–61.
- Patti MG, Diener U, Tamburini A, Molena D, Way LW. 2001. Role of esophageal function tests in diagnosis of gastroesophageal reflux disease. *Dig Dis Sci* 46(3):597–602.
- Pavone P, Laghi A, Catalano C, Cardone G, Messina A, Neri T, Basso N, Passariello R. 1997. CT of nissen's fundoplication. *Abdom Imaging* 22(5):457–60.
- Pearson FG, Langer B, Henderson RD. 1971. Gastroplasty and belsey hiatus hernia repair. an operation for the management of peptic stricture with acquired short esophagus. *J Thorac Cardiovasc Surg* 61(1):50–63.

- Peery AF, Crockett SD, Barritt AS, Dellon ES, Eluri S, Gangarosa LM, Jensen ET, Lund JL, Pasricha S, Runge T, et al. 2015. Burden of gastrointestinal, liver, and pancreatic diseases in the united states. *Gastroenterology* 149(7):1731,1741.e3.
- Penagini R and Bravi I. 2010. The role of delayed gastric emptying and impaired oesophageal body motility. *Best Pract Res Clin Gastroenterol* 24(6):831–45.
- Pugliese D, Mauro A, Consonni D, Bravi I, Tenca A, Elvevi A, Conte D, Penagini R. 2016. pH impedance vs. traditional pH monitoring in clinical practice: An outcome study. *J Gastroenterol* 51(2):130–7.
- Ranson ME, Danielson A, Maxwell JG, Harris JA. 2007. Prospective study of laparoscopic nissen fundoplication in a community hospital and its effect on typical, atypical, and nonspecific gastrointestinal symptoms. *JLS* 11(1):66–71.
- Rantanen TK, Halme TV, Luostarinen ME, Karhumaki LM, Kononen EO, Isolauri JO. 1999. The long term results of open antireflux surgery in a community-based health care center. *Am J Gastroenterol* 94(7):1777–81.
- Rantanen TK, Oksala NKJ, Oksala AK, Salo JA, Sihvo EIT. 2008. Complications in antireflux surgery: National-based analysis of laparoscopic and open fundoplications. *Arch Surg* 143(4):359–65.
- Reading A. 1989. Testing pain mechanisms in persons in pain. In: *Textbook of pain*. Wall P and Melzack R, editors. 2nd ed. Churchill Livingstone Inc, New York. 269 p.
- Revicki DA, Wood M, Maton PN, Sorensen S. 1998a. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med* 104(3):252–8.
- Revicki DA, Wood M, Wiklund I, Crawley J. 1998b. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. *Qual Life Res* 7(1):75–83.
- Rijnhart-De Jong HG, Draaisma WA, Smout AJPM, Broeders IAMJ, Gooszen HG. 2008. The visick score: A good measure for the overall effect of antireflux surgery?. *Scand J Gastroenterol* 43(7):787–93.
- Robinson B, Dunst CM, Cassera MA, Reavis KM, Sharata A, Swanstrom LL. 2015. 20 years later: Laparoscopic fundoplication durability. *Surg Endosc* 29(9):2520–4.
- Ronkainen J, Aro P, Storskrubb T, Johansson S, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Talley NJ, Agreus L. 2005a. Prevalence of barrett’s esophagus in the general population: An endoscopic study. *Gastroenterology* 129(6):1825–31.
- Ronkainen J, Aro P, Storskrubb T, Johansson S, Lind T, Bolling-Sternevald E, Graffner H, Vieth M, Stolte M, Engstrand L, et al. 2005b. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult swedish population: A kalixanda study report. *Scand J Gastroenterol* 40(3):275–85.
- Rossetti M and Hell K. 1977. Fundoplication for the treatment of gastroesophageal reflux in hiatal hernia. *World J Surg* 1(4):439–43.
- Ruigomez A, Garcia Rodriguez LA, Wallander M, Johansson S, Eklund S. 2006. Esophageal stricture: Incidence, treatment patterns, and recurrence rate. *Am J Gastroenterol* 101(12):2685–92.
- Salminen JT, Salo JA, Tuominen JA, Ramo OJ, Farkkila M, Mattila SP. 1997. pH-metric analysis after successful antireflux surgery: Comparison of 24-hour pH profiles in patients undergoing floppy fundoplication or roux-en-Y duodenal diversion. *J Gastrointest Surg* 1(6):494–8.
- Salminen P, Hurme S, Ovaska J. 2012. Fifteen-year outcome of laparoscopic and open nissen fundoplication: A randomized clinical trial. *Ann Thorac Surg* 93(1):228–33.

- Salminen PTP, Hiekkänen HI, Rantala APT, Ovaska JT. 2007. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: A prospective randomized study with an 11-year follow-up. *Ann Surg* 246(2):201–6.
- Salo JA, Ala-Kulju KV, Heikkinen LO, Kivilaakso EO. 1991. Treatment of severe peptic esophageal stricture with roux-en-Y partial gastrectomy, vagotomy, and endoscopic dilation. A follow-up study. *J Thorac Cardiovasc Surg* 101(4):649–53.
- Sandbu R, Khamis H, Gustavsson S, Haglund U. 2002. Laparoscopic antireflux surgery in routine hospital care. *Scand J Gastroenterol* 37(2):132–7.
- Sandbu R and Sundbom M. 2010. Nationwide survey of long-term results of laparoscopic antireflux surgery in Sweden. *Scand J Gastroenterol* 45(1):15–20.
- Savarino E, Zentilin P, Tutuian R, Pohl D, Casa DD, Frazzoni M, Cestari R, Savarino V. 2008. The role of nonacid reflux in NERD: Lessons learned from impedance-pH monitoring in 150 patients off therapy. *Am J Gastroenterol* 103(11):2685–93.
- Savary M and Miller G. 1977. *Der Ösophagus. Lehrbuch und endoskopischer atlas*. Solothurn, Switzerland: Gassmann.
- Schindlbeck NE, Heinrich C, König A, Dendorfer A, Pace F, Müller-Lissner SA. 1987. Optimal thresholds, sensitivity, and specificity of long-term pH-metry for the detection of gastroesophageal reflux disease. *Gastroenterology* 93(1):85–90.
- Schwarz GS. 1967. Historical aspects of the anatomy of the cardia with special reference to hiatus hernia. *Bull N Y Acad Med* 43(2):112–25.
- Sharma P, Dent J, Armstrong D, Bergman, Jacques J G H M., Gossner L, Hoshihara Y, Jankowski JA, Junghard O, Lundell L, Tytgat GNJ, et al. 2006. The development and validation of an endoscopic grading system for Barrett's esophagus: The Prague C & M criteria. *Gastroenterology* 131(5):1392–9.
- Shaw JM, Bornman PC, Callanan MD, Beckingham IJ, Metz DC. 2010. Long-term outcome of laparoscopic nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: A prospective, randomized trial. *Surg Endosc* 24(4):924–32.
- Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N, Zhang X, Adhami T, Murray J, Peters J, et al. 2004. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: A multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterol* 99(6):1037–43.
- Sifrim D, Castell D, Dent J, Kahrilas PJ. 2004. Gastro-oesophageal reflux monitoring: Review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 53(7):1024–31.
- Sikkema M, Looman CWN, Steyerberg EW, Kerkhof M, Kastelein F, van Dekken H, van Vuuren AJ, Bode WA, van der Valk H, Ouwendijk RJT, et al. 2011. Predictors for neoplastic progression in patients with Barrett's esophagus: A prospective cohort study. *Am J Gastroenterol* 106(7):1231–8.
- Sintonen H. 2001. The 15D instrument of health-related quality of life: Properties and applications. *Ann Med* 33(5):328–36.
- Skinner DB and Belsey RH. 1967. Surgical management of esophageal reflux and hiatus hernia. long-term results with 1,030 patients. *J Thorac Cardiovasc Surg* 53(1):33–54.
- Somasekar K, Morris-Stiff G, Al-Madfai H, Barton K, Hassn A. 2010. Is a bougie required for the performance of the fundal wrap during laparoscopic nissen fundoplication?. *Surg Endosc* 24(2):390–4.
- Sontag SJ, Sonnenberg A, Schnell TG, Leya J, Metz A. 2006. The long-term natural history of gastroesophageal reflux disease. *J Clin Gastroenterol* 40(5):398–404.

- Soresi AL. 1919. Diaphragmatic hernia: Its unsuspected frequency: Its diagnosis: Technic for radical cure. *Ann Surg* 69(3):254–70.
- Soricelli E, Basso N, Genco A, Cipriano M. 2009. Long-term results of hiatal hernia mesh repair and antireflux laparoscopic surgery. *Surg Endosc* 23(11):2499-504.
- Soudagar AS, Sayuk GS, Gyawali CP. 2012. Learners favour high resolution oesophageal manometry with better diagnostic accuracy over conventional line tracings. *Gut* 61(6):798–803.
- Spechler SJ. 2004. The management of patients who have “failed” antireflux surgery. *Am J Gastroenterol* 99(3):552–61.
- Srivastava A, Golden KL, Sanchez CA, Liu K, Fong PY, Li X, Cowan DS, Rabinovitch PS, Reid BJ, Blount PL, et al. 2015. High goblet cell count is inversely associated with ploidy abnormalities and risk of adenocarcinoma in barrett’s esophagus. *PLoS ONE [Electronic Resource]* 10(7):e0133403.
- Stadlhuber RJ, Sherif AE, Mittal SK, Fitzgibbons RJJ, Michael Brunt L, Hunter JG, Demeester TR, Swanstrom LL, Daniel Smith C, Filipi CJ. 2009. Mesh complications after prosthetic reinforcement of hiatal closure: A 28-case series. *Surg Endosc* 23(6):1219–26.
- Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD, SAGES Guidelines Committee. 2010. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 24(11):2647–69.
- Stein HJ, Eypasch EP, DeMeester TR, Smyrk TC, Attwood SE. 1990. Circadian esophageal motor function in patients with gastroesophageal reflux disease. *Surgery* 108(4):769–77.
- Stein HJ, Barlow AP, DeMeester TR, Hinder RA. 1992a. Complications of gastroesophageal reflux disease. role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and duodenogastric reflux. *Ann Surg* 216(1):35–43.
- Stein HJ, Barlow AP, DeMeester TR, Hinder RA. 1992b. Complications of gastroesophageal reflux disease. role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and duodenogastric reflux. *Ann Surg* 216(1):35–43.
- Stein HJ, Feussner H, Siewert JR. 1996. Failure of antireflux surgery: Causes and management strategies. *Am J Surg* 171(1):36–9.
- Sweet R. 1950. Diaphragmatic hernia. In: *Thoracic surgery*. Sweet R, editor. Philadelphia: WB Saunders, 316–334.
- Tatum RP, Soares RV, Figueredo E, Oelschlager BK, Pellegrini CA. 2010. High-resolution manometry in evaluation of factors responsible for fundoplication failure. *J Am Coll Surg* 210(5):611–7.
- Terry ML, Vernon A, Hunter JG. 2004. Stapled-wedge collis gastroplasty for the shortened esophagus. *Am J Surg* 188(2):195–9.
- Tosato F, Marano S, Mattacchione S, Luongo B, Mingarelli V, Campagna G. 2012. Quality of life after nissen-rossetti fundoplication. *Surg Laparosc Endosc Percutan Tech* 22(3):205–9.
- Toupet MA. 1963. Technique d’oesophago-gastroplastic avec phreno-gastropexie appliquee dans la cure radicale des hernies hiatales et comme complement de l’operation de heller dans les cordiospasmes. *Mémoires. Académie De Chirurgie* 89:394–9.
- Triantos C, Koukias N, Karamanolis G, Thomopoulos K. 2015. Changes in the esophageal mucosa of patients with non erosive reflux disease: How far have we gone? *World J Gastroenterol* 21(19):5762–7.
- Trus TL, Bax T, Richardson WS, Branum GD, Mauren SJ, Swanstrom LL, Hunter JG. 1997. Complications of laparoscopic paraesophageal hernia repair. *J Gastrointest Surg* 1(3):221–7.

- Tucker LE, Blatt C, Richardson NL, Richardson DT, Cassat JD, Riechers TB. 2005. Laparoscopic nissen fundoplication in a community hospital: Patient satisfaction survey. *South Med J* 98(4):441–3.
- Tuttle SG, Rufin F, Bettarello A. 1961. The physiology of heartburn. *Ann Intern Med* 55:292–300.
- Ukleja A, Woodward TA, Achem SR. 2002. Vagus nerve injury with severe diarrhea after laparoscopic antireflux surgery. *Dig Dis Sci* 47(7):1590–3.
- Vakil N, Shaw M, Kirby R. 2003. Clinical effectiveness of laparoscopic fundoplication in a U.S. community. *Am J Med* 114(1):1–5.
- Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. 2006. The montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. *Am J Gastroenterol* 101(8):1900–20.
- Vakil NB, Halling K, Becher A, Ryden A. 2013. Systematic review of patient-reported outcome instruments for gastroesophageal reflux disease symptoms. *Eur J Gastroenterol Hepatol* 25(1):2–14.
- Varban OA, McCoy TP, Westcott C. 2011. A comparison of pre-operative comorbidities and post-operative outcomes among patients undergoing laparoscopic nissen fundoplication at high- and low-volume centers. *J Gastrointest Surg* 15(7):1121–7.
- Velanovich V. 1998. Comparison of generic (SF-36) vs. disease-specific (GERD-HRQL) quality-of-life scales for gastroesophageal reflux disease. *J Gastrointest Surg* 2(2):141–5.
- Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di Mario F, Battaglia G, Mela GS, Pilotto A. 1995. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 333(17):1106–10.
- Viljakka M, Luostarinen M, Isolauri J. 1997. Incidence of antireflux surgery in finland 1988–1993. influence of proton-pump inhibitors and laparoscopic technique. *Scand J Gastroenterol* 32(5):415–8.
- Viljakka M, Saali K, Koskinen M, Karhumaki L, Kossi J, Luostarinen M, Teerenhovi O, Isolauri J. 1999. Antireflux surgery enhances gastric emptying. *Arch Surg* 134(1):18–21.
- Visick AH. 1948. Measured radical gastrectomy; review of 505 operations for peptic ulcer. *Lancet* 1(6501):505.
- Voutilainen M, Farkkila M, Mecklin JP, Juhola M, Sipponen P. 2000. Classical barrett esophagus contrasted with barrett-type epithelium at normal-appearing esophagogastric junction. central finland endoscopy study group. *Scand J Gastroenterol* 35(1):2–9.
- Wang W, Huang M, Wei P, Lee W. 2008. Laparoscopic antireflux surgery for the elderly: A surgical and quality-of-life study. *Surg Today* 38(4):305–10.
- Wani S, Falk G, Hall M, Gaddam S, Wang A, Gupta N, Singh M, Singh V, Chuang K, Boolchand V, et al. 2011. Patients with nondysplastic barrett’s esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 9(3):220–7.
- Ware JJ, Snow K, Kosinski M, Gandek B. 1993. SF-36 health survey: Manual and interpretation guide. Boston: The Health Institute, New England Medical Center.
- Watson DI, Jamieson GG, Devitt PG, Mitchell PC, Game PA. 1995. Paraesophageal hiatus hernia: An important complication of laparoscopic nissen fundoplication. *Br J Surg* 82(4):521–3.
- Watson DI, Baigrie RJ, Jamieson GG. 1996. A learning curve for laparoscopic fundoplication. definable, avoidable, or a waste of time?. *Ann Surg* 224(2):198–203.
- Weigt J, Monkemuller K, Peitz U, Malfertheiner P. 2007. Multichannel intraluminal impedance and pH-metry for investigation of symptomatic gastroesophageal reflux disease. *Dig Dis* 25(3):179–82.

- Weijenborg PW, Cremonini F, Smout AJPM, Bredenoord AJ. 2012. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: A meta-analysis. *Neurogastroenterol Motil* 24(8):747–57.
- Westerhoff M, Hovan L, Lee C, Hart J. 2012. Effects of dropping the requirement for goblet cells from the diagnosis of Barrett's esophagus. *Clin Gastroenterol Hepatol* 10(11):1232–6.
- Williams VA, Watson TJ, Gellersen O, Feuerlein S, Molena D, Sillin LF, Jones C, Peters JH. 2007. Gastrectomy as a remedial operation for failed fundoplication. *J Gastrointest Surg* 11(1):29–35.
- Winklestein A. 1935. Peptic esophagitis (a new clinical entity). *JAMA* (104):906.
- Xenos ES, Reinker D, Mogerman D. 2001. Early experience with laparoscopic antireflux surgery in the rural setting. *South Med J* 94(1):43–6.
- Yang H, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. 2008. Randomized trial of division versus nondivision of the short gastric vessels during laparoscopic nissen fundoplication: 10-year outcomes. *Ann Surg* 247(1):38–42.
- Yang H, Meun C, Sun X, Watson DI. 2012. Outcome following management of dysphagia after laparoscopic anti-reflux surgery. *World J Surg* 36(4):838–43.
- Zak Y and Rattner DW. 2016. The use of LINX for gastroesophageal reflux. *Adv Surg* 50(1):41–8.
- Zaninotto G, DeMeester TR, Schwizer W, Johansson KE, Cheng SC. 1988. The lower esophageal sphincter in health and disease. *Am J Surg* 155(1):104–11.
- Zaninotto G, Parente P, Salvador R, Farinati F, Tieppo C, Passuello N, Zanatta L, Fassan M, Cavallin F, Costantini M, et al. 2012. Long-term follow-up of Barrett's epithelium: Medical versus antireflux surgical therapy. *J Gastrointest Surg* 16(1):7–14.
- Zerbib F, Bruley des Varannes S, Simon M, Galmiche JP. 2012. Functional heartburn: Definition and management strategies. *Curr Gastroenterol Rep* 14(3):181–8.
- Zerbib F, Sifrim D, Tutuian R, Attwood S, Lundell L. 2013. Modern medical and surgical management of difficult-to-treat GORD. *United European Gastroenterol J* 1(1):21–31.
- Zhou T, Harnsberger C, Broderick R, Fuchs H, Talamini M, Jacobsen G, Horgan S, Chang D, Sandler B. 2015. Reoperation rates after laparoscopic fundoplication. *Surg Endosc* 29(3):510–4.
- Åkerlund Å, Onnell H, Key E. 1926. Hernia diaphragmatica hiatus oesophagei vom anatomischen und roentgenologischen gesichtspunkt. *Acta Radiologica* (6):3–22.

12 ORIGINAL PUBLICATIONS

THE IMPACT OF FIBRIN GLUE IN THE PREVENTION OF FAILURE AFTER NISSEN FUNDOPLICATION

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ABSTRACT

Background and Aims: Good long term result after Nissen fundoplication is achieved in most of the patients in specialized centres. Still failure occurs in some cases and reoperation after failed conservative treatment is done in 3–6% of the cases. Reoperation is more dangerous and results worse than after primary fundoplication. Therefore we wanted to analyze factors related to failure of Nissen fundoplication with special emphasis on utilization of crural closure, anchoring of the fundic wrap and the use of fibrin glue.

Material and Methods: Patients records of 258 patients were analyzed by an independent observer. Defective fundic wrap, recurrent oesophagitis and hiatal hernia were defined as failure.

Results: Failure after Nissen fundoplication was found in 29 patients (14.9%). Crural closure ($p = 0.021$), anchoring of the wrap ($p = 0.020$) and fibrin glue ($p = 0.029$) decreased the incidence of failure. However, only crural closure ($p = 0.010$) and fibrin glue ($p = 0.019$) were independent factors in the prevention of failure.

Conclusions: Fibrin glue as a new method might be worth utilizing to further decrease the incidence of failure after Nissen fundoplication. Because our study was retrospective, prospective randomized study should be performed before universal use of fibrin glue in the prevention of failure after fundoplication.

Key words: Defective fundic wrap; oesophagitis; failure; fibrin glue; crural closure; fundoplication

INTRODUCTION

Nissen fundoplication performed due to gastro-oesophageal reflux disease (GERD) heals oesophagitis, improves reflux symptoms and may diminish the length of Barrett's epithelium or even abolish it (1, 2).

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In Finland, the majority of fundoplications are performed outside university clinics (3). Although the results of Nissen fundoplication in specialized centres have been good, the results in nonspecialized centres have not been well documented. Only a few studies have dealt with the results of antireflux surgery in community hospitals (4–9), and there is little data on the long-term results using objective investigation methods (5). Long-term results of open Nissen fundoplication performed in our hospital during 1980–1992 were somewhat worse than in a teaching hospital (10). This was attributed mainly to the infrequency of the operation, leading to use of several different modifications of Nissen fundoplication. In the same

study, 30% of patients with recurrent esophagitis had a normal fundic wrap, suggesting impaired oesophageal peristalsis.

According to retrospective, uncontrolled studies crural closure, anchoring of the wrap and fundic mobilization have been found to be crucial in the prevention of failure (11–13). In addition, the routine use of a bougie has been found to decrease severe postoperative dysphagia, although more postoperative dilatations were done among patients with bougie (14). However, the effect of fibrin glue in humans on the failure rate after Nissen fundoplication has not been investigated previously.

The aim of this study was to analyze the possible reasons for failure after Nissen fundoplication in a community hospital with special emphasis on the effect of crural closure, anchoring of the wrap and the use of fibrin glue.

MATERIAL AND METHODS

The study population comprised all patients ($n = 269$) operated on for GERD from January 1991 to December 2000 at Kanta-Häme Central Hospital (population, approximately 178000). Pre- and postoperative data was analysed retrospectively by one of the authors (P.N.) who had not been involved in the patients' care. Nine patients were operated using Toupet's partial fundoplication (15) due to oesophageal dysmotility found in manometry and two patients using the technique of Russel (16) because their reflux disease was associated with duodenal ulcer disease. Our analysis of operative technique focuses on Nissen fundoplication and the total number of patients operated using the technique of Nissen was 258. The mean follow-up was 61.5 months (range 21–137 months). The mean age of these 150 men (58.1%) and 108 women (41.9%) was 53 years (range 17–85). The mean duration of GERD symptoms before the operation was 86.5 months, and median use of preoperative antireflux medication was 30 months.

Preoperative evaluation consisted of upper gastrointestinal endoscopy in 256 (2 had barium swallow) patients, 24-hour pH-monitoring in 224 (mean $\text{pH} < 4$ 19.7%, range 0.3–97%; pathological in 204 cases), and oesophageal manometry (17, 18) in 203 (mean LES-pressure 12.7mmHg, range 0–43mmHg). In manometry isolated abnormal peristalsis was found in 45 cases, abnormal LES relaxation in five cases and both abnormal peristalsis and abnormal LES relaxation in three cases (19). Savary-Miller grading of the oesophageal mucosa (20) was used (grade 0, 78 cases; grade I, 74; grade II, 54; grade III, 25 and grade IV, 27 cases) preoperatively but postoperatively grade of oesophagitis was not mentioned in most of the cases and therefore Savary-Miller classification has not been used after operation.

Preoperatively all patients had either reflux symptoms or symptoms related to hiatal hernia (vomiting, dyspnea or abdominal or chest pain) (21) and also pathological findings in pH-monitoring, endoscopy or barium swallow.

Postoperatively all patients were directed to upper gastrointestinal endoscopy six months after operation and it was also done to patients with postoperative symptoms suggestive for failures. Endoscopy was agreed by 195 patients (75.6%). Fundic wrap was classified as defective if a distinct gastric pouch above the narrowing caused by the folds of the wrap could be found (slipped Nissen) or there was no visible folds (total disruption) or only distorted, loose folds (partial disruption) at the oesophagogastric

junction. If a gap beside of fundic wrap was found a recurrent hiatal hernia was recorded. Recurrent oesophagitis and/or defective fundic wrap or recurrent hiatal hernia were classified as failure.

Among 201 patients fundoplication was started with the laparoscopic technique, but in 24 (11.9%) cases conversion to open surgery was necessary due to intraoperative problems. Originally 57 operations were performed using an open technique. The reasons for choosing the open technique were operations done by surgeons who did not perform laparoscopic procedures (43 cases), some other procedure demanding open technique (seven cases) and large mixed type hiatal hernia or paraoesophageal hernia (seven cases). This study was approved by the ethical committee of Kanta-Häme Central Hospital.

STATISTICAL METHODS

Univariate analyse using Chi-square test was made for statistical comparisons as indicated. In addition, multiple logistic regression model was used to find out independent factors related with failure. $P < 0.05$ was considered as significant.

RESULTS

During the study period 258 Nissen fundoplications were performed by 12 surgeons (mean 21.5 per surgeon, range 1–124) with a significant increase in operations per year ($p = 0.034$) (Figure 1).

Nasogastric tube was used for calibrating fundic wrap in 134 cases (52%), while endoscope was used in 46 cases (17.8%) and 48 or 52 French bougie in 78 cases (30.2%). Fundic mobilization was done in 58 cases (22.5%), crural closure in 137 cases (53%) and anchoring of the wrap in 196 cases (76%). In addition, fibrin glue (Tissell duo quick, 2ml, Baxter) was used in fundic wrap (fibrin glue was injected between serosal folds) in 138 cases (53.5%). Among 237 patients (91.9%) fundic wrap was done with three or four non-absorbable stitches. Anchoring of the wrap ($p = 0.002$) and crural closure ($p < 0.001$) increased significantly from 1991 to 2000 (Figure 2).

Failure was detected in 29 (14.9%) patients with no differences between open (9; 15.8%) and laparoscopic (15; 8.5%) technique. Failure was found in five (20.8%) patients after conversion.

According to univariate analysis the incidence of failure was significantly lower among patients with crural closure ($p = 0.021$), anchoring of the fundic wrap ($p = 0.020$) and fibrin glue ($p = 0.029$) (Table 1). Age, sex, severe preoperatively found oesophagitis, large hiatal hernia, dysmotility, the use of bougie or fundic mobilization had no effect on the failure rate. However, in multivariate analysis only crural closure ($p = 0.010$) and fibrin glue ($p = 0.019$) decreased significantly the incidence of failure.

Reoperation was done only for ten patients (incidence 3.9%). The incidence of reoperation did not correlate with any specific factor. Technical details on the primary operation and type of failure found during reoperation are shown in Table 2.

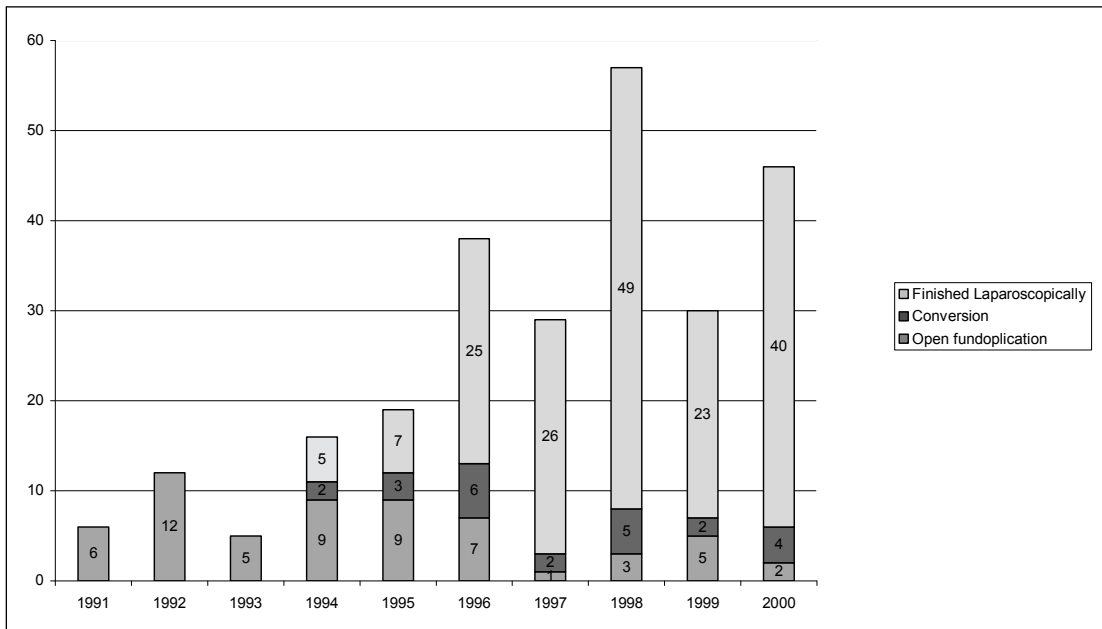


Fig. 1. The annual number of performed laparoscopic and open Nissen funduplications

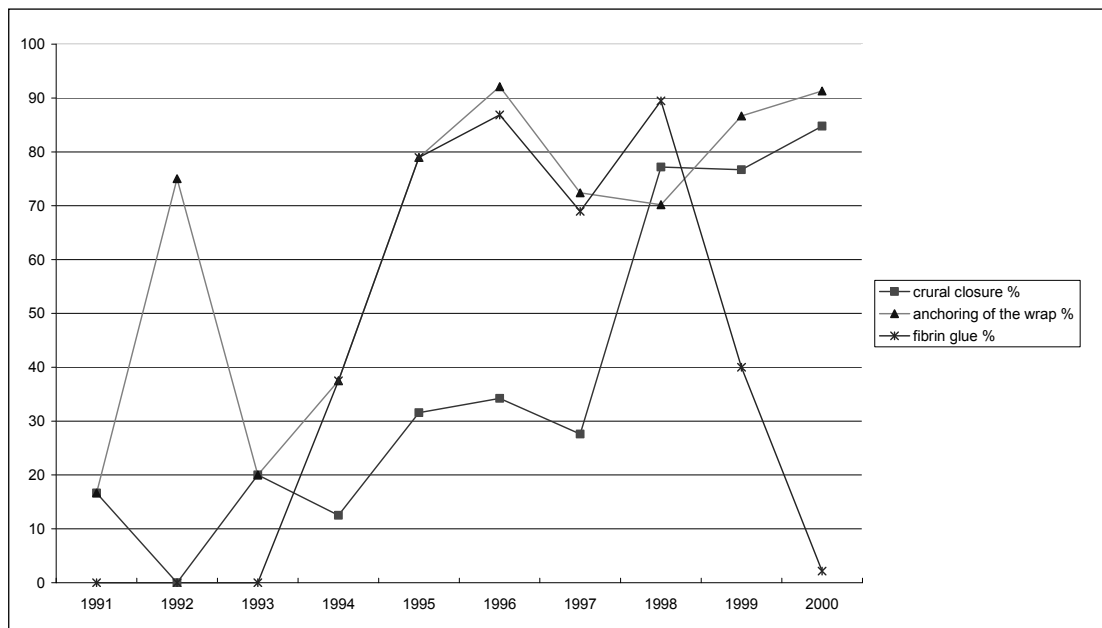


Fig. 2. The annual percentages of the use of crural closure, anchoring of the wrap and fibrin glue.

DISCUSSION

The incidence of failure during mid term follow-up in the present study was comparable to the earlier reports from specialized centres and community hospitals. Our results could have been worse because many surgeons did these operations and most of them also did their learning curve phase in our hospital. Probably the good results were achieved by following strictly the important technical aspects of Nissen fundoplication, including crural closure.

TABLE 1

The incidence of crural closure, anchoring of the wrap and fibrin glue among patients with different type of failures

Patient group	Crural closure	Anchoring	Fibrin glue
Oesophagitis (n = 9)	1 (11.1%)	2 (22.2%)	2 (22.2%)
Oesophagitis and Defective wrap (n = 3)	0	0	0
Defective wrap (n = 17)	8 (47%)	15 (88%)	8 (47%)

TABLE 2

Details of primary operation and type of failure during second operation among patients with reoperation

Patient	Lap/Open	Mobilization	Crural closure	Anchoring	Type of Failure
I	Open	Yes	No	No	Slipped Nissen
II	Open	No	No	No	Slipped Nissen
III	Lap	No	No	No	Disruption and intrathoracic herniation
IV	Open	No	Yes	Yes	Paraoesophageal herniation
V	Lap	No	No	No	Slipped Nissen
VI	Lap	No	Yes	Yes	Slipped Nissen
VII*	Lap	No	Yes	Yes	Corpoplication
VIII*	Lap	No	Yes	Yes	Slipped Nissen
IX*	Lap	No	Yes	Yes	Too tight wrap
X*	Lap	No	Yes	Yes	Too tight wrap

* Reoperations were done because of severe dysphagia unresponsive to dilatations

Slight modifications of Nissen fundoplication include fundic mobilization and the use of oesophageal bougie when during fundic wrapping, which have been found to reduce postoperative symptoms and probably also lessen the risk of wrap disruption (22–24). In the present study, these procedures were not found to affect failure rate or severe dysphagia (data not shown). However, the number of cases with fundic mobilization was small and therefore type II error can not be excluded.

In the same unit during 1980's the anchoring of the wrap was used only in 30% of the patients and this was probably the main reason for the high number of slipping (5). In the present study anchoring the wrap, crural closure and fibrin glue decreased the incidence of failure. However, only crural closure and fibrin glue were found to be independent factors in the prevention of failure. Previously crural closure has been found to be crucial in the technique of laparoscopic Nissen fundoplication, otherwise the incidence of postoperative paraoesophageal hernia has been found to increase (12). To our knowledge this is the first study in humans reporting decreasing effect of fibrin glue on failure after Nissen fundoplication. According to an experimental animal study fibrin glue was the only method that caused scar formation between serosal folds of the fundic wrap and the authors concluded that fibrin glue could reduce the incidence of failures of fundoplication (25). Thereafter fibrin glue was used in our hospital during six years' period, and its use was terminated mainly due to fear of increased incidence of dysphagia, although in the present study no evidence of such (data not shown) could be found. This study reports results from a community hospital, where many surgeons with different experience performed these operations. However, fibrin glue might be worth trying to further reduce the risk of failure of fundoplication also in specialized centres, where recurrent oesophagitis and defective fundic wraps have been found in 3–17% (10, 22) and 22.9–28.6% (10, 26) of the patients, respectively.

The weaknesses of the study are due to retrospective setting. Therefore some factors related to failure may not be assessed reliably. However, the main factors of the technique of Nissen fundoplication could be easily detected. Our analysis was performed by an objective observer, which can be considered as a ben-

efit. The second drawback of the present study is that analysis was made using patient records. Therefore some asymptomatic patients with failure might have been missed. All revisional oesophageal surgery in the region was done at our hospital. This makes it highly unlikely that any further operations or serious postoperative problems would be unknown to us. Final criticism to our study is that we used endoscopically defined criteria for failure and not 24-hour pH-recording and therefore we do not know exactly the amount of acid exposure. However, in only 3% of the asymptomatic patients with intact fundic wrap abnormal 24-hour pH-monitoring is found (27). Therefore we think that most of failures in the present study have been found. However, further study analysing long term results by objective methods, including interview, endoscopy and pH-monitoring is needed to detect possible late failures after fundoplication.

In conclusion, crural closure and fibrin glue were found to decrease the incidence of failure after fundoplication and these procedures might be worth using in other centres too. However, the effect of fibrin glue on failure of Nissen fundoplication should be investigated using prospective randomized study before its use in other centres, because our study was retrospective.

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REFERENCES

1. Rantanen T, Salo J, Salminen J, et al: Functional outcome after laparoscopic or open Nissen fundoplication: a follow-up study. *Arch Surg* 1999;134:240–244
2. DeMeester T: Antireflux surgery in the management of Barrett's esophagus. *J Gastrointest Surg* 2000;4(2):24–128
3. Viljakka M, Luostarinen M, Isolauri J: Incidence of antireflux surgery in Finland 1988–1993. Influence of proton-pump in-

- hibitors and laparoscopic technique. *Scand J Gastroenterol* 1997;32(5):415-418
4. Leggett P, Churchman-Winn R, Ahn C: Resolving gastroesophageal reflux with laparoscopic fundoplication. *Surg Endosc* 1998;12(2):142-147
 5. Rantanen T, Halme T, Luostarinen M, et al: The long term results of open antireflux surgery in a community-based health care center. *Am J Gastroenterol* 1999;94:1777-1781
 6. Voitk A, Joffe J, Alvarez C, et al: Factors contributing to laparoscopic failure during the learning curve for laparoscopic Nissen fundoplication in a community hospital. *J Laparoendosc Adv Surg Tech A* 1999;9(3):243-248
 7. Vakil N, Shaw M, Kirby R: Clinical effectiveness of laparoscopic fundoplication in a U.S. community. *Am J Med* 2003; 114(1):1-5
 8. Hwang H, Turner L, Blair N: Examining the learning curve of laparoscopic fundoplications at an urban community hospital. *Am J Surg* 2005;189(5):522-526
 9. Tucker L, Blatt C, Richardson N, et al: Laparoscopic Nissen fundoplication in a community hospital: patient satisfaction survey. *South Med J* 2005;98(4):441-443
 10. Luostarinen M: Nissen fundoplication for reflux esophagitis. Long-term clinical and endoscopic results in 109 out of 127 consecutive patients. *Ann Surg* 1993;217(4):329-337
 11. Siewert J, Isolauri J, Feussner H: Reoperation following failed fundoplication. *World J Surg* 1989;13:791-797
 12. Watson D, Jamieson G, DeVitt P, et al: Paraesophageal hiatus hernia: an important complication of laparoscopic Nissen fundoplication. *Br J Surg* 1995;82(4):521-523
 13. Stein H, Feussner H, Siewert J: Failure of antireflux surgery: causes and management strategies. *Am J Surg* 1996;171:36-40
 14. Patterson E, Herron D, Ramzi N, et al: Effect of an esophageal bougie on the incidence of dysphagia following nissen fundoplication: a prospective, blinded, randomized clinical trial. *Arch Surg* 2000;135(9):1055-1061
 15. Toupet A: Technique d'oesophago-gastroplastie avec phrèno-gastropexie appliquée dans la cure radicale des hernies hiatales et comme complément de l'opération de Heller dans les cardiospasmés. *Acad Chir* 1963; 89:394-399
 16. Russell R: Abdominal repair of oesophageal hiatus hernia. In: Dudley H, Rob C, Smith R, editors, *Operative Surgery*, Third edition, 1977;166-171
 17. DeMeester T, Johnson L, Joseph G, et al: Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 1976;184(4): 459-470
 18. DeMeester T, Johnson L: The evaluation of objective measurements of gastroesophageal reflux and their contribution to patients management. *Surg Clin North Am* 1976;56(1):39-53
 19. Stein H, DeMeester T: Indications, technique, and clinical use of ambulatory 24-hour esophageal motility monitoring in a surgical practice. *Ann Surg* 1993;217(2):128-137
 20. Savary M, Miller G: *Der oesophagus, lehrbuch und endoskopischer atlas*. Solothurn: Gassmann, 1977
 21. Sihvo E, Salo J, Räsänen J, et al: Fatal complications of adult paraesophageal hernia: a population-based study. *J Thorac Cardiovasc Surg* 2009;137(2):419-424
 22. Donahue P, Samelson S, Nyhus L, et al: The floppy Nissen fundoplication. *Arch Surg* 1985;120:663-668
 23. DeMeester T, Bonavina L, Albertolucci M: Nissen fundoplication for gastroesophageal reflux disease. *Ann Surg* 1986;204:9-20
 24. Siewert J, Feussner H, Walker S: Fundoplication: how to do it? Periesophageal wrapping as a therapeutic principal in gastroesophageal reflux. *World J Surg* 1992;16:326-334
 25. Isolauri J, Viljakka M, Helin H, et al: Disruption of experimental fundic folds is prevented by interserosal scarring. *Br J Surg* 1997;84(4):548-550
 26. Luostarinen M, Isolauri J, Laitinen J, et al: Fate of Nissen fundoplication after 20 years. A clinical, endoscopic and functional analysis. *Gut* 1993;34:1015-1020
 27. O'Hanrahan T, Marples M, Bancewicz J: Recurrent reflux and wrap disruption after Nissen fundoplication: detection, incidence and timing. *Br J Surg* 1990;77:545-547

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Health-Related Quality of Life 10 Years After Laparoscopic Nissen Fundoplication—Results of a Community-Based Hospital

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Abstract

Background: The lack of correlation between the symptomatic outcome after fundoplication and the results of objective measurements has been demonstrated. Therefore, subjective tools are needed to measure the outcomes of the treatment. Long-term results concerning health-related quality of life (HRQoL) after laparoscopic Nissen fundoplication (LNF) performed in a community-based hospital are lacking. The objective of this study was to describe HRQoL of an LNF cohort 10 years after surgery performed in a community-based hospital.

Subjects and Methods: In 1997–1999, 107 LNFs were performed. The 15D questionnaire was mailed to all patients, and consent to participate in the study was requested. The patients who agreed to participate were interviewed. The resulting 15D profile and single index scores were compared with those of a sample of age-standardized general population ($n=6053$).

Results: Of the 107 patients, 64 (59.8%) participated in the study (40 men; mean age, 61.9 years; range, 28–85 years). The mean 15D score for our patient group was 0.860 versus 0.888 for the age-standardized general population ($P=.030$). The mean 15D score of the patients who were satisfied with the surgical results was 0.870 (median, 0.890), which is clinically the same as that of the general population. Among the patients, dissatisfaction with the results of surgery decreased the mean 15D score by 0.069 ($P=.023$).

Conclusions: Our long-term follow-up study suggests that, in the majority of patients, HRQoL after LNF performed in a community-based hospital is similar to that of the general population, while the subjective failure of surgery leads to suboptimal results. The multidimensional 15D instrument seems a promising HRQoL instrument also when applied to gastroesophageal reflux disease patients.

Introduction

CHARACTERISTIC OF GASTROESOPHAGEAL reflux disease (GERD) is that its symptoms cause discomfort and lower the patient's health-related quality of life (HRQoL).¹ Even though proton pump inhibitors (PPIs) are potent in healing esophageal mucosal damage, approximately 30% of the patients fail medical therapy.² Furthermore, many patients are not satisfied with continuous medical treatment.³

Laparoscopic antireflux surgery has been found equally effective as medical therapy when treating patients with objectively verified reflux initially responsive to PPI therapy.⁴ However, in clinical practice, the patient group is often not as

highly selected as that of the previous study. The common indication for surgery is refractory GERD.⁵⁻⁷ The mechanisms behind the symptoms of GERD patients are diverse and not always possible to verify objectively. The lack of correlation between the symptomatic outcome after surgery and the results of objective measurements has been demonstrated.^{8,9} Therefore, subjective tools such as HRQoL instruments are needed to measure the outcomes of the treatment. Previously, the HRQoL of GERD patients waiting for an antireflux operation has been verified as being significantly decreased.⁶ The measurement of HRQoL by a generic instrument, like 15D or EQ-5D, make it possible to clarify quality-adjusted life years, which further can be used for

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measurement of the cost-effectiveness of laparoscopic Nissen fundoplication (LNF).¹⁰ This is important when considering either lifetime medication with PPIs or LNF among patients with chronic GERD.

The objective of the current study was to describe the HRQoL of an LNF cohort 10 years after surgery performed in a community-based hospital. A comparison between our patient group and the general Finnish population was conducted using the 15D instrument. No prior long-term follow-up studies after LNF using a multidimensional HRQoL instrument have been published. In addition, we found no report dealing with long-term results concerning HRQoL after LNF performed in a community-based hospital.

Subjects and Methods

In the Kanta-Häme Central Hospital (Hämeenlinna, Finland), 121 funduplications were performed during 1997–1999. The year 1996 was the first when the majority of antireflux procedures were performed by using LNF. We decided to focus on the following years (1997–1999) to avoid a possible learning curve bias. Partial and open funduplications were excluded, but laparoscopic procedures that had been converted to open operations were included. The total number of LNFs during the 3-year period was 107. The operative technique has been described previously.¹¹ The indications for surgery were typical symptoms or dissatisfaction with medical treatment as well as objectively verified GERD as diagnosed by means of gastrointestinal endoscopy, 24-hour pH monitoring, and esophageal manometry.

The 15D is a generic, comprehensive HRQoL instrument that can be used as a profile and single index score measure. The 15D dimensions are as follows: breathing, mental function, speech (communication), vision, mobility, usual activities, vitality, hearing, eating, excretion, sleeping, distress, discomfort and symptoms, sexual activity, and depression. Each dimension is divided into five levels by which the attribute is distinguished. The single index score (15D score) representing the overall HRQoL on a scale of 0–1 (where 1 = full health and 0 = being dead) and the dimension level values reflecting the goodness of the levels relative to no problems in the dimension (= 1) and to being dead (= 0) are calculated from the health status descriptive system by using a set of population-based preference of utility weights.

A change or difference of approximately 0.03 in the 15D score is considered clinically important in the sense that people can, on average, feel the difference.¹²

The 15D data for the general population came from the National Health 2000 Health Examination Survey, which covered a representative sample of the Finnish population (age-standardized *n* = 6053).¹³

The 15D questionnaire was mailed to all the patients, with a request for consent to participate in the study. The patients who agreed were interviewed in 2008–2009 by a nurse who had not been previously involved in the patients' care.

The few missing data on the dimensions were replaced using regression analysis by having the dimension with missing data as the dependent variable and the other dimensions as well as age and sex as independent variables. The differences between the two groups' mean (median) 15D scores and dimension level values were tested using an independent-samples *t* test (Mann–Whitney U test). To explore the extent to which a lung disorder

and dissatisfaction with the results of surgery might affect the 15D score, a regression model was run with the 15D score as the dependent variable and age, sex, lung disorder (0=no, 1=yes), and dissatisfaction with the results of surgery (0=no, 1=yes) as explanatory variables. A *P* value of <.05 was considered statistically significant.

This study was approved by the ethical committee of the Kanta-Häme Central Hospital.

Results

Sixty-four (59.8%) of the 107 patients participated in the study (40 men; mean age, 61.9 years; range, 28–85 years). The participation rate among the still-living patients was 66.7% (64 of the 96 patients). Twenty-eight (26.1%) patients refused to participate, failed to attend, or could not be contacted, whereas 11 (10.3%) had died of causes not related to GERD or LNF, and 4 were immobile (3.7%). The patient records of the 43 nonparticipating patients were reviewed, and neither late complications nor re-operations were detected. The patient characteristics of the study population and of the nonattending patients are described in Table 1. The mean duration of GERD symptoms before the operation was 92.3 months, and median use of preoperative antireflux medication was 40 months. Of the subjects, 89.1% used PPIs preoperatively, whereas 7.8% used H2-receptor antagonists. The mean follow-up time was 9.8 years. Nine patients (14.1%) reported having a lung disorder, the prevalence of which is higher than what is found in the general Finnish population.¹⁴ Otherwise, the morbidity was comparable to the general population.

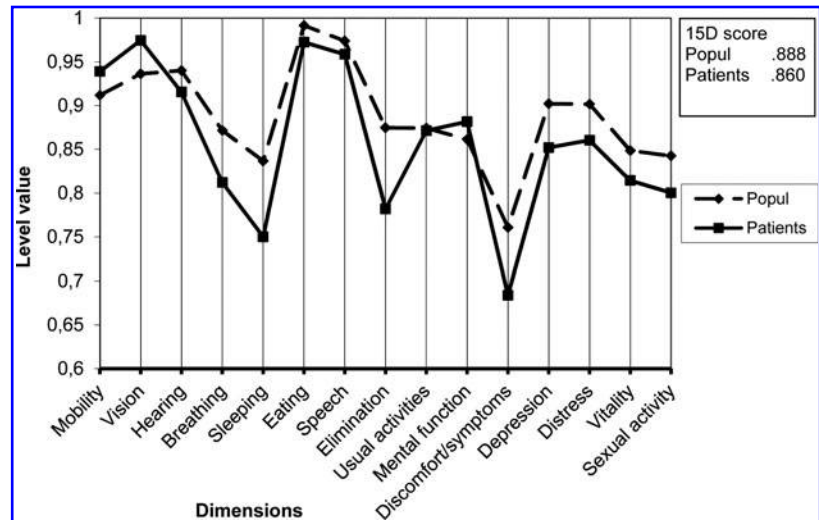
Three (4.7%) patients had undergone re-operations. Four (6.3%) primary procedures had been converted to open funduplications. Six (9.4%) patients required continuous PPI medication, 17 (26.6%) had taken PPIs occasionally, and 41 (64.1%) had not needed PPIs. Fifty-seven (89.1%) patients would have chosen surgery as a treatment again if they were to have the same kind of symptoms as preoperatively. Four (6.3%) patients would not have chosen surgery again, and 3 (4.7%) were undecided. Fifty-three (82.8%) patients were satisfied with the results of the surgery, 4 (6.3%) were dissatisfied, and 7 (10.9%) were unsure about their opinion. Dysphagia was the most common (8 of the 11 patients; 72.7%) reason for dissatisfaction (data not shown). However, only 1 dissatisfied patient thought that the preoperative situation had been better than the postoperative one. Three of the dissatisfied individuals felt the operation had not benefited them. Four of those 7 who were ambivalent concerning the results felt that the postoperative situation was better, and 1 felt that the postoperative situation was worse than the preoperative one.

TABLE 1. PATIENT CHARACTERISTICS

<i>Characteristic</i>	<i>Study population</i>	<i>Nonattending patients</i>
Age at operation (years)		
Mean	52.0	54.8
Median	53.7	54.1
Male gender (%)	62.5%	62.8%
Preoperative BMI (kg/m ²)	27.0	28.0

BMI, body mass index.

FIG. 1. The 15D profiles and scores of gastroesophageal reflux disease patients 10 years after laparoscopic Nissen fundoplication performed in a community-based hospital and of an age-standardized general population (Popul).



The mean 15D score for our patient group was 0.860 versus 0.888 for the age-standardized general population. The difference is statistically significant ($P = .030$) and clinically important (Fig. 1). There were no differences between men and women in the mean 15D score or in any of the individual dimensions. The patient group’s mean dimension level values for breathing, sleeping, excretion, discomfort and symptoms, and depression were lower than those of the age-standardized general population (Table 2). Contrary to these dimensions, the scores for vision were higher in the patient group (Table 2). In addition, there was a statistically significant difference in the median level value for the dimensions of eating, distress, and vitality. The mean 15D score of the patients who were satisfied with the surgical results was 0.870 (median, 0.890), which is clinically the same as that of the general population.

The regression analysis indicated that when age, sex, and dissatisfaction with the results of surgery were standardized, a lung disorder decreased the mean 15D score by 0.068 ($P = .039$).

When age, sex, and lung disorder were standardized, dissatisfaction with the treatment decreased the mean 15D score by 0.069 ($P = .023$). Therefore, subjective failure of the treatment was found to be a reducing factor in HRQoL.

Discussion

Our long-term results show that the mean HRQoL (15D score) of the LNF cohort is slightly lower than that of the

age-standardized general population. However, the mean 15D score among those who were satisfied with the results of surgery is close to that of the general population. In fact, the scores of the satisfied and the general population are clinically the same. The results of the present study indicate that, after subjectively successful LNF, a normal level of HRQoL can still be maintained after 10 years. To our knowledge, this is the first long-term follow-up study after LNF using a generic, preference-based multidimensional HRQoL instrument. In addition, there are no previous long-term reports concerning quality of life after LNF performed in a community-based hospital.

The lack of correlation between objective measurements of GERD and patient-perceived symptoms makes HRQoL an important variable in assessing the results of LNF. HRQoL can be defined as the patients’ subjective perception of the impact of their disease and its treatment on daily life as well as on physical, psychological, and social functioning and well-being.¹⁵ There are several disease-specific and generic instruments for evaluating the HRQoL of GERD patients. The measurement of HRQoL is complex, and it has been suggested that the multidimensional term HRQoL is often misinterpreted.¹⁶ The disease-specific instruments generally focus on diseases, symptoms, and adverse events without actual multidimensional HRQoL questions, whereas generic instruments may be too insensitive to detect changes in an individual’s state of health in the case of a disease whose effect on the quality of life is limited.^{16,17}

Previously, improvements in the HRQoL have been reported after LNF.^{18–20} Many studies have applied the Gastrointestinal Quality of Life Index to measure the HRQoL after fundoplication.^{5,18–20} The results have been close to those of healthy individuals, but no comparison with a general population has been published. The Gastrointestinal Quality of Life Index has been criticized for not meeting the criteria for multidimensionality and, therefore, not assessing the HRQoL in its entirety.¹⁵ Anvari and Allen²¹ used the Short Form-36 to assess the HRQoL of patient groups consisting of poor and good responders to PPI therapy over a 5-year period after LNF; an improvement was observed in both groups, but the mean postoperative scores were subtly lower than those of the North American general population. In a study by Velanovich,¹⁷ it was shown that the Short

TABLE 2. STATISTICALLY SIGNIFICANT DIFFERENCES IN MEAN 15D SCORES

Dimension	Study population (n = 64)	Age-standardized general population (n = 6053)
Mean 15D score ($P = .030$)	0.860	0.888
Breathing ($P = .049$)	0.812	0.872
Sleeping ($P = .000$)	0.750	0.837
Excretion ($P = .000$)	0.782	0.875
Discomfort and symptoms ($P = .003$)	0.684	0.761
Depression ($P = .007$)	0.852	0.902
Vision ($P = .008$)	0.975	0.936

Form-36 has poor discriminatory power for satisfied and dissatisfied patients with GERD and is inferior to the GERD-HRQoL in measuring the symptom severity in GERD.

The mean 15D score of our whole patient group was slightly lower than that of the general population. Our results also suggest that with the effect of age, sex, and lung disorder standardized, the mean 15D score of those dissatisfied with the results of surgery was clearly lower (−0.069) than that of the satisfied subjects. Most of the dissatisfied patients suffered from dysphagia. To minimize postoperative dysphagia, the operative technique includes now dividing two or three of the uppermost short gastric vessels to make it possible to do a loose fundic wrap more easily. It is likely that patients with suboptimal outcomes or substantial side effects from the treatment may feel dissatisfied and thus experience lowered HRQoL. In addition, a lung disorder seems to clearly decrease the mean 15D score (−0.068).

In our study, the 15D was able to discriminate between the satisfied and the dissatisfied subjects. This implies that despite being a generic instrument, 15D is sensitive enough to detect differences in the states of health of GERD patients. Our results come from a community-based hospital, but the discrimination power of 15D allows the comparison of results between other hospitals. Prior studies have found the instrument highly responsive to treatment-related changes with many other diseases,^{12,22–24} and as regards the other most important properties (reliability, discriminatory power), the 15D performs at least equally to similar types of generic HRQoL instruments and is well validated.^{12,25} The instrument also meets the criterion of multidimensionality and allows us to make age-standardized comparisons between the patients and the general population.

The lack of preoperative 15D scores is a limitation that prevented us from evaluating the effects of the treatment directly. We refer to the previously published results that have found significant impairments in the HRQoL of GERD patients using both generic and disease-specific instruments.^{6,18,19,21,26} In addition to GERD-related symptoms, the candidates for surgery are troubled by ineffective medical treatment and are anxious about their illness or GERD complications.¹⁸ Therefore, the effectiveness of a treatment in terms of the HRQoL can be assessed by comparing a patient group's HRQoL with that of the general population. Another limitation of the current study is that the participation rate was only 59.8% (or 66.7% when taking only still-living patients into account). However, we reviewed the patient records of the nonparticipating patients, and neither late complications nor re-operations were detected. Because our hospital is the only unit performing re-funduplications in the area, it is likely that patients with major difficulties would have been found. The known demographic characteristics of the nonattending patients are similar to the study population (Table 1), which supports our assumption that there is no selection bias. In addition, our response rate among patients who are alive is well comparable to the REFLUX¹⁰ and LOTUS⁴ trials (68.9% and 72.5% at 5 years, respectively). Finally, our study is retrospective, and therefore all aspects cannot be reliably evaluated. Until the results of prospective, randomized, long-term follow-up studies dealing with HRQoL are ready, our study from a community-based hospital gives important information for clinicians about the quality of life after LNF when deciding whether a patient with chronic GERD should be

operated on or not. However, to our knowledge those prospective studies concerning quality of life after LNF are using other instruments, such as EQ-5D, instead of 15D.²⁷ The results of HRQoL varies depending on what instrument is used.²⁸ Therefore our results as such cannot be compared with those of other HRQoL studies.

In conclusion, we noted in our long-term follow-up study that the HRQoL of the majority of patients after LNF performed in a community-based hospital is similar to the general population, whereas the subjective failure of surgery leads to suboptimal results. The multidimensional 15D instrument seems a promising HRQoL instrument also when applied to GERD patients and thus may be used for analysis of cost-effectiveness of LNF. The cost-effectiveness of LNF is an important factor, when considering either lifetime PPI therapy or LNF among patients with chronic GERD.

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Disclosure Statement

No competing financial interests exist.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900–1920.
2. Chey W, Mody R, Izat E. Patient and physician satisfaction with proton pump inhibitors (PPIs): Are there opportunities for improvement? *Dig Dis Sci* 2010;55:3415–3422.
3. Kahrilas P, Howden C, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. *Am J Gastroenterol* 2011;106:1419–1425.
4. Galmiche JP, Hatlebakk J, Attwood S, Ell C, Fiocca R, Eklund S, Långström G, Lind T, Lundell L. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: The LOTUS randomized clinical trial. *JAMA* 2011;305:1969–1977.
5. Rosenthal R, Peterli R, Guenin MO, von Flüe M, Ackermann C. Laparoscopic antireflux surgery: Long-term outcomes and quality of life. *J Laparoendosc Adv Surg Tech A* 2006;16:557–561.
6. Heikkinen T, Koivukangas V, Wiik H, Saarnio J, Rautio T, Haukipuro K. The quality of life of gastroesophageal reflux disease patients waiting for an antireflux operation. *Surg Endosc* 2004;18:1712–1715.
7. Rantanen T, Kiljander T, Salminen P, Ranta A, Oksala N, Kellokumpu I. Reflux symptoms and side effects among patients with gastroesophageal reflux disease at baseline, during treatment with PPIs, and after Nissen fundoplication. *World J Surg* 2013;37:1291–1296.
8. Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional Nissen fundoplication: A prospective randomized study with an 11-year follow-up. *Ann Surg* 2007;246:201–206.

9. Luostarinen M. Nissen fundoplication for reflux esophagitis. Long-term clinical and endoscopic results in 109 of 127 consecutive patients. *Ann Surg* 1993;217:329–337.
10. Faria R, Bojke L, Epstein D, Corbacho B, Sculpher M. Cost-effectiveness of laparoscopic fundoplication versus continued medical management for the treatment of gastro-oesophageal reflux disease based on long-term follow-up of the REFLUX trial. *Br J Surg* 2013;100:1205–1213.
11. Rantanen T, Neuvonen P, Iivonen M, Tomminen T, Oksala N. The impact of fibrin glue in the prevention of failure after Nissen fundoplication. *Scand J Surg* 2011;100:181–185.
12. Sintonen H. The 15D instrument of health-related quality of life: Properties and applications. *Ann Med* 2001;33:328–336.
13. Aromaa A, Koskinen S (eds). Health and functional capacity in Finland. Baseline results of the Health 2000 Health Examination Survey. Publication B12/2004. Helsinki: National Public Health Institute, 2004.
14. Pallasaho P, Lundbäck B, Läspä SL, Jönsson E, Kotaniemi J, Sovijärvi A, Laitinen L. Increasing prevalence of asthma but not of chronic bronchitis in Finland? Report from the FinEsS-Helsinki Study. *Respir Med* 1999;93:798–809.
15. European Agency for the Evaluation of Medicinal Products. Committee for Medicinal Products for Human Use. Reflection paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products. 2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guide_line/2009/09/WC500003637.pdf (accessed February 4, 2014).
16. Chassany O, Holtmann G, Malagelada J, Gebauer U, Doerfler H, Devault K. Systematic review: Health-related quality of life (HRQL) questionnaires in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008;27:1053–1070.
17. Velanovich V. Comparison of generic (SF-36) vs. disease-specific (GERD-HRQL) quality-of-life scales for gastro-oesophageal reflux disease. *J Gastrointest Surg* 1998;2:141–145.
18. Kamolz T, Granderath PA, Bammer T, Pasiut M, Wykypiel H, Herrmann R, Pointner R. Mid- and long-term quality of life assessments after laparoscopic fundoplication and re-fundoplication: A single unit review of more than 500 antireflux procedures. *Dig Liver Dis* 2002;34:470–476.
19. Fein M, Bueter M, Thalheimer A, Pachmayr V, Heimbucher J, Freys S, Fuchs K. Ten-year outcome of laparoscopic antireflux surgery. *J Gastrointest Surg* 2008;12:1893–1899.
20. Dallemagne B, Weerts J, Markiewicz S, Dewandre J, Wahlen C, Monami B, Jehaes C. Clinical results of laparoscopic fundoplication at ten years after surgery. *Surg Endosc* 2006;20:159–165.
21. Anvari M, Allen C. Surgical outcome in gastro-esophageal reflux disease patients with inadequate response to proton pump inhibitors. *Surg Endosc* 2003;17:1029–1035.
22. Malmivaara A, Hakkinen U, Aro T, Heinrichs M, Koskenniemi L, Kuusama E, Lappi S, Paloheimo R, Servo C, Vaaranen V, Hernberg S. The treatment of acute low back pain—Bed rest, exercises, or ordinary activity? *N Engl J Med* 1995;332:351–355.
23. Kauppinen R, Sintonen H, Tukiainen H. One-year economic evaluation of intensive vs. conventional patient education and supervision for selfmanagement of new asthmatic patients. *Respir Med* 1998;92:300–307.
24. Stavem K. Reliability, validity and responsiveness of two multiattribute utility measures in patients with chronic obstructive pulmonary disease. *Qual Life Res* 1999;8:45–54.
25. Hawthorne G, Richardson J, Day N. A comparison of the assessment of quality of life (AQoL) with four other generic utility instruments. *Ann Med* 2001;33:358–370.
26. Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med* 1998;104:252–258.
27. Grant A, Cotton S, Boachie C, Ramsay C, Krukowski Z, Heading R, Campbell M. Minimal access surgery compared with medical management for gastro-oesophageal reflux disease: Five year follow-up of a randomised controlled trial (REFLUX). *BMJ* 2013;346:f1908.
28. Goeree R, Hopkins R, Marshall J, Armstrong D, Ungar W, Goldsmith C, Allen C, Anvari M. Cost-utility of laparoscopic Nissen fundoplication versus proton pump inhibitors for chronic and controlled gastroesophageal reflux disease: A 3-year prospective randomized controlled trial and economic evaluation. *Value Health* 2011;14:263–273.

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Endoscopic Evaluation of Laparoscopic Nissen Fundoplication: 89 % Success Rate 10 Years After Surgery

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Abstract

Background The surgical outcome of fundoplication can be evaluated by means of esophagogastroduodenoscopy (EGDS). The literature reveals only one prior long-term follow-up series with endoscopic evaluation of the fundoplication wraps after laparoscopic Nissen fundoplication (LNF). The results achieved at a university clinic showed LNF to be more durable than open fundoplication (ONF). Previously, in our community-based hospital, the results of ONF were somewhat poorer than those achieved at a university clinic. The objective of the present study was to describe the long-term results of LNF in our hospital as regards surgical and symptomatic outcomes.

Methods In 1997–1999, 107 LNFs were performed in our hospital. A questionnaire with symptom evaluation was mailed to all patients. The patients who agreed to participate were interviewed and underwent EGDS.

Results Of the 107 patients, 64 (59.8 %) participated in the study (40 men, mean age 61.9 years, range 28–85 years). The mean follow-up time was 9.8 years. Seven endoscopic examinations (10.9 %) showed a defective fundic wrap; three of the patients had undergone reoperation. Fifty-eight (90.6 %) patients had no or minimal heartburn and 61 (95.3 %) had no or minimal regurgitation. Twenty-three (35.9 %) patients had moderate or severe dysphagia, and 43 (67.2 %) patients had moderate or severe flatulence. Fifty-seven (89.1 %) patients would have opted for surgery again.

Conclusions This study contributes to the previous notion that LNF is associated with fewer surgical failures than ONF. Our results indicate that LNF can well be performed in a community-based hospital with acceptable long-term results.

Introduction

Gastroesophageal reflux disease (GERD) is a common condition in Western countries, and in many cases, it is a chronic disease. In a severe form of GERD, the treatment options are life-long maintenance therapy with proton pump inhibitors (PPIs) or laparoscopic Nissen fundoplication (LNF) [1]. Neither PPIs nor LNF can prevent the development of esophageal adenocarcinoma [2, 3], the prevalence of which has been shown to be increasing among patients with GERD [4]. Therefore, the main goal in the treatment of chronic GERD patients is to prevent GERD symptoms.

It has proven difficult to define failure after fundoplication [5, 6]. Discrepancies have been found between subjective symptomatic outcomes and objective measurements [7–9]. Still, the sheer surgical outcome and durability of the fundoplication wrap can be evaluated, as the

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anatomic appearance of a fundoplication wrap can be seen on esophagogastroduodenoscopy (EGDS). In prior follow-up studies, high numbers of defective fundic wraps (23, 37, and 46.4 %) have been found after open Nissen fundoplication (ONF) [7, 9, 10]. The follow-up times have varied considerably (3.1–9.2, 1–15, and 12.8–17.3 years), but a clear trend toward a higher incidence of defects, increasing with the length of follow-up, has been noted. The results from our community-based hospital were poorer than those of a university clinic after ONF [10].

A literature review revealed only one prior long-term follow-up series—reporting results 11 and 15 years post-operatively—with an endoscopic evaluation of fundic wraps after LNF [7, 11]. The disruption rate of the wraps in the LNF group was significantly lower than in the ONF group (11.1 vs. 46.4 % after 15 years), suggesting more durable results for LNF. The study reported the results from a university clinic. The objective of the present study was to describe the long-term results of LNF performed in a community-based hospital as regards surgical and symptomatic outcomes. To the best of our knowledge, no prior studies reporting the long-term results from a community-based hospital with an endoscopic evaluation of fundic wrap have been published.

Materials and methods

Between 1997 and 1999, 121 antireflux operations were performed at the Kanta-Häme Central Hospital. In the late 1990s the number of other antireflux procedures became so low that we decided to focus on LNF. The year 1996 was the first when LNF was the predominant antireflux procedure [12]. To minimize possible learning curve issues, we decided to study the following 3-year period. With partial and open fundoplications excluded, a total of 107 laparoscopically initiated Nissen fundoplications were performed during that period. The procedures were performed by four surgeons whose respective operation rates were 59, 42, 19, and 5. One of the surgeons was a resident. At the time of surgery, the mean age of the patients was 53.2 years (range 16–85 years). Sixty-six (61.7 %) of the patients were men.

The primary symptoms of the patients were heartburn (74.8 %), regurgitation or vomiting (11.2 %), dysphagia (5.6 %), abdominal pain (3.7 %), and extraesophageal symptoms (1.9 %). GERD was objectively verified in all cases. All patients underwent preoperative gastrointestinal endoscopy; 24 h pH monitoring was performed for 103 (96.3 %) and esophageal manometry for 101 (94.4 %) patients.

The operative technique varied to some extent. The proportions of different variations used, as well as conversion rates, are listed in Table 1. In the majority of cases,

Table 1 The proportions of technical variations used and the conversion rates

Technical variation	Study population (<i>n</i> = 64) (%)	All patients (<i>n</i> = 107) (%)
Hiatoplasty	60.9	64.4
Anchoring of the wrap	76.6	74.8
Fundus mobilization	7.8	12.1
Fibrin glue	78.1	72.9
Conversion	6.3	8.4

hiatoplasty, anchoring of the wrap, and fibrin glue (Tisseel Duo Quick, 2 ml, Baxter AG, Vienna, Austria) were used. Mobilization of the fundus was performed only in a minority of cases. A nasogastric tube, endoscope, or either a 48 or a 52 French bougie was routinely used for calibrating the fundic wrap.

The DeMeester symptom scores were applied for the evaluation of heartburn, regurgitation, and dysphagia [13]. Flatulence and bloating were analyzed with a similar 4-point scale. The patients were asked to evaluate both their preoperative state and their current condition with regard to every symptom. In addition, the patients were requested to state their satisfaction level with their preoperative condition (satisfied, undecided, unsatisfied) and with the results of surgery. They were also asked if they would still prefer surgical treatment to medical treatment if they were to have same the kind of symptoms as preoperatively. Patients were also asked about the possible postoperative use of acid-suppressing drugs and operative procedures (reoperations, dilatations).

All patients were mailed the forms containing the above-mentioned items, and their consent to participate in the study was requested. The patients who agreed were interviewed in 2008–2009 by a nurse who had not been previously involved in the patients' care. The form was completed in detail in cooperation with the nurse.

Two of the authors (M.I. and T.R.) performed upper gastrointestinal endoscopy on the patients after the interview. Their particular interest was in the endoscopic appearance of the fundic wrap, but signs of esophagitis, Barrett's esophagus, and hiatal hernia were also noted. The fundic wrap was classified as defective if a distinct gastric pouch above the narrowing caused by the folds of the wrap could be observed (slipped Nissen), or if there were no visible folds (total disruption) or only distorted, loose folds (partial disruption) at the esophagogastric junction. If a gap was found beside the fundic wrap, a recurrent hiatal hernia was recorded. A defective fundic wrap was classified as a surgical failure. All of the wraps were photographed and the photographs were analyzed later in conjunction with the other authors.

Statistical methods

The Chi-square test, Mann–Whitney *U* test, and Wilcoxon signed rank test were used for statistical comparisons. Statistical analyses were performed with SPSS version 19.0 (SPSS inc., Chicago, IL, USA). *P* values <0.05 were considered statistically significant.

Results

Sixty-four (59.8 %) of the initial 107 patients participated in the study (40 men, mean age 61.9 years; range 28–85 years). Twenty-eight (26.1 %) patients refused to participate, failed to attend, or could not be contacted, 11 (10.3 %) had died of causes unknown to us, and 4 were immobile (3.7 %) (Fig. 1). The patient records of the 43 non-participating patients were reviewed, and neither late complications nor reoperations were detected. The patient characteristics of the study population and of the non-attending patients are described in Table 2. The mean follow-up time was 9.8 years.

Surgical failure was detected in seven (10.9 %) endoscopies (slipped Nissen in six patients, disruption in one). Esophagitis was detected in four patients, two of whom had surgical failure. The incidence of esophagitis was significantly higher in patients with surgical failure ($P = 0.010$). Surgical failure was statistically more prevalent among patients in whom fibrin glue was not used ($P = 0.036$).

Anchoring of the wrap had not been performed in two, and fibrin glue was not used in four of those six patients with slipped Nissen. One patient had slipped Nissen in spite of anchoring of the wrap and the use of fibrin glue.

The patients with surgical failure reported more heartburn ($P = 0.004$) and regurgitation ($P = 0.012$) than patients with an intact fundoplication wrap. There was no difference in dysphagia, bloating, and flatulence between the patients with defective and intact fundoplication wraps.

The use of antisecretory medication did not correlate with the prevalence of esophagitis ($P = 0.099$); instead, there was a correlation between the use of antisecretory medication and surgical failure. If a patient had used antisecretory medication at some point, the risk of surgical failure was 12 times higher than in cases where medication had not been used ($P = 0.031$). Furthermore, if a patient used continuous antisecretory medication, surgical failure was 20 times more likely ($P = 0.025$).

Table 2 Patient characteristics

Characteristic	Study population	Non-attending patients
Mean age at operation (years)	52.0	54.8
Median age at operation (years)	53.7	54.1
Male gender (%)	62.5	62.8
Preoperative BMI	27.0 kg/m ²	28.0 kg/m ²

BMI body mass index

Fig. 1 Study profile

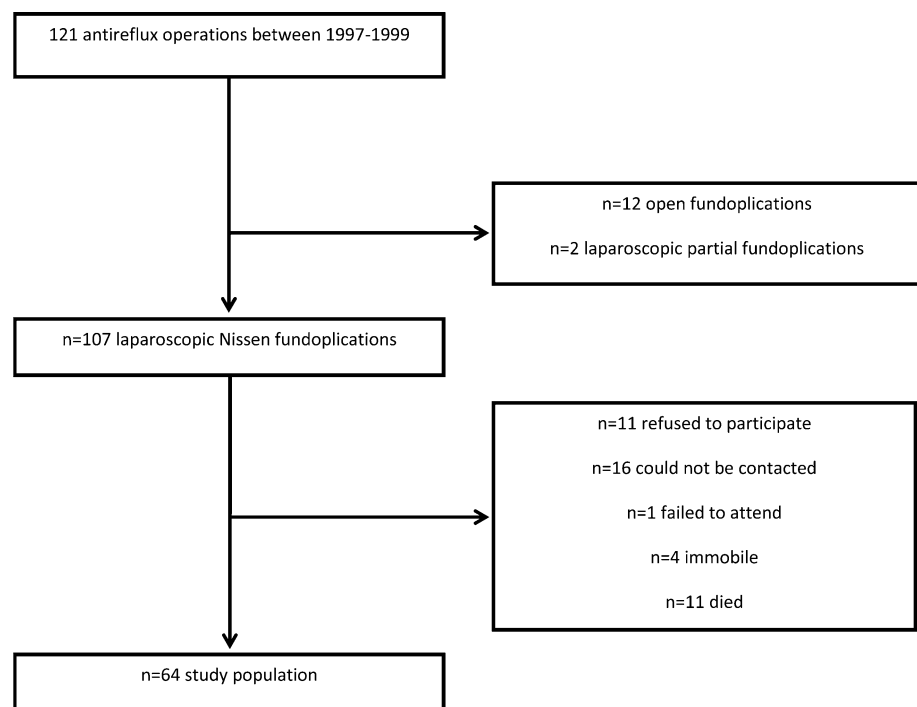
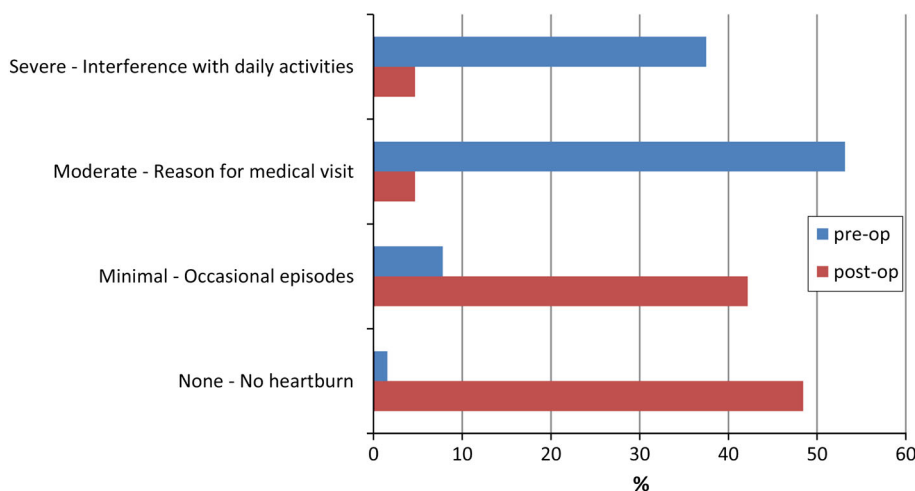
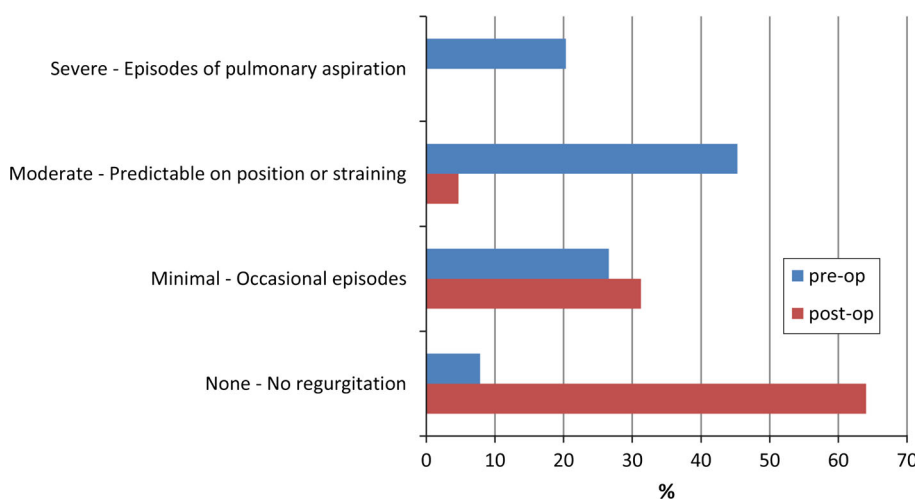


Fig. 2 Self-rated change in heartburn**Fig. 3** Self-rated change in regurgitation

Three of 64 (4.7 %) patients had undergone reoperation: two for an endoscopically verified slipped Nissen and symptom recurrence and one for dysphagia and weight loss. Besides the one patient who had undergone reoperation for dysphagia, 5 of 64 (7.8 %) patients had required dilatation to correct postoperative dysphagia, and one patient (1.6 %) required dilatation for ventricle retention (pyloric dilatation). One patient had undergone dilatation six times, one two times, and three once. No dilatations were performed on the non-attending patients in our hospital. Three (4.7 %) patients had required postoperative hernia repair, and one (1.2 %) patient had suffered a fundic perforation from a non-absorbed suture. Six (9.4 %) patients were on continuous antisecretory medication, 17 (26.6 %) had taken medication at some point, and 41 (64.1 %) had not needed it.

The primary symptoms had resolved significantly: 58 (90.6 %) patients had none or only minimal heartburn ($P < 0.001$) (Fig. 2), and 61 (95.3 %) patients had none or only minimal regurgitation ($P < 0.001$) (Fig. 3).

Dysphagia had increased ($P = 0.026$): 41 patients (64.1 %) had no or only minimal dysphagia, 21 (32.8 %) had moderate dysphagia, and two (3.1 %) suffered from severe dysphagia (Fig. 4). Fundic mobilization was performed in only five (7.8 %) patients, four of whom had no dysphagia and one only minimal dysphagia. The use of fibrin glue was not associated with postoperative dysphagia.

There was no statistical difference between preoperative and postoperative bloating (Fig. 5), but flatulence had increased ($P = 0.024$) (Fig. 6). Forty-three (67.2 %) patients reported moderate or severe flatulence. Fifty-seven (89.1 %) patients would have chosen surgery as a treatment again if they were to develop the same kind of symptoms as preoperatively. Four (6.3 %) patients would not have chosen surgery again, and three (4.7 %) were undecided. The patient satisfaction increased significantly after the operation ($P < 0.001$). Preoperatively, one (1.6 %) patient had been satisfied with his/her condition, five (7.8 %) had been undecided, and 58 (90.6 %) had been unsatisfied. Postoperatively, 53 (82.8 %) patients were satisfied with the results of the surgery, four

Fig. 4 Self-rated change in dysphagia

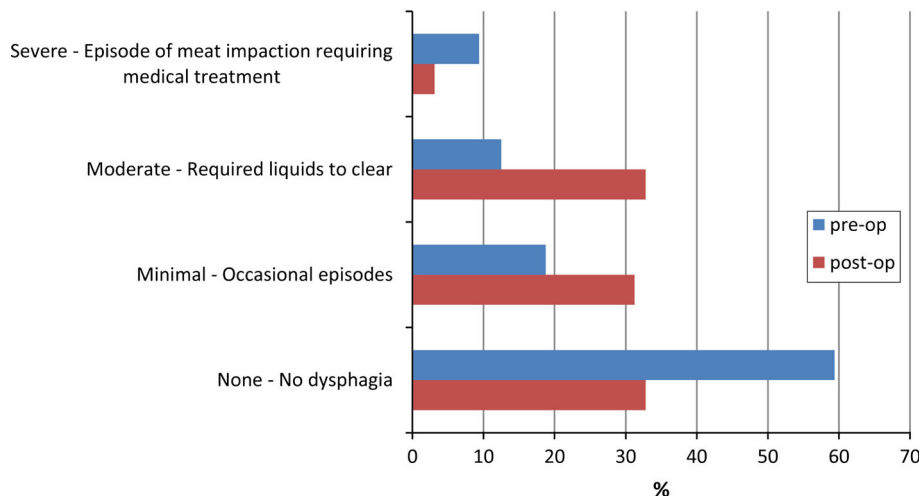


Fig. 5 Self-rated change in bloating

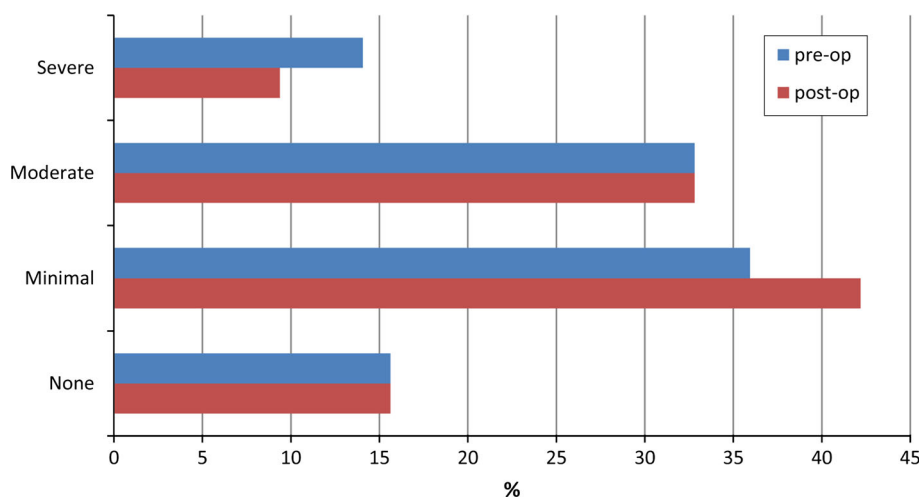
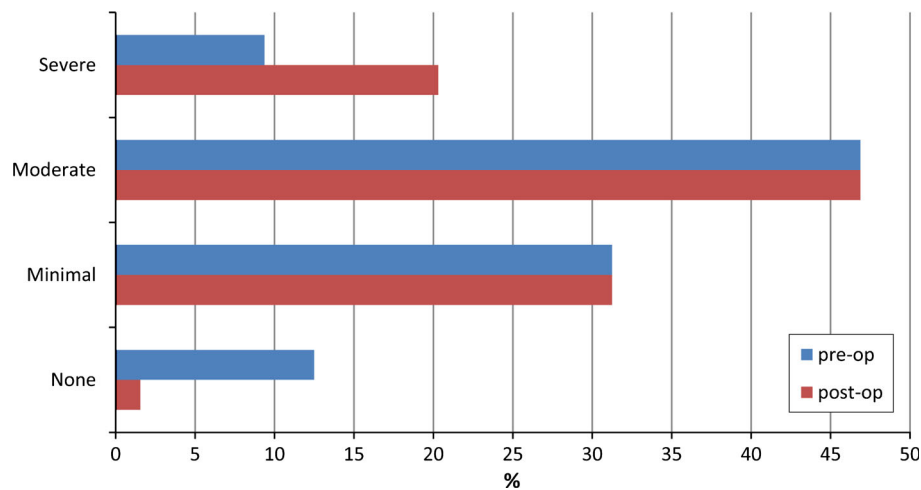


Fig. 6 Self-rated change in flatulence



(6.3 %) were unsatisfied, and seven (10.9 %) were undecided. With the above-mentioned scale, only two patients felt the preoperative situation was better than the postoperative situation.

Discussion

In our study, surgical failure defined as a defective fundic wrap was detected in only 10.9 % of the patients. These

results concerning defective fundic wraps are well comparable to the results of a university clinic and contribute to the assumption that LNF is more durable than ONF in long-term follow-up.

Previously, high numbers of surgical failures after ONF have been observed. After 6.5 years (1–15 years) of follow-up, 37 % of the ONF wraps were found defective in our hospital [10]. A clear trend toward an increase in the incidence of defects with the length of follow-up has been linked to ONF [7, 9]. Still, there is only one prior long-term follow-up series with endoscopic evaluation of the fundoplication wraps. Laparoscopic Nissen fundoplication was found more durable than ONF, as surgical failure was more prevalent after ONF (46.4 vs. 11.1 %, respectively). In that series, the proportion of defective wraps increased further between 11 and 15 years of follow-up in the ONF group but not in the LNF group [7, 11]. The present results for LNF are also clearly better than the previous results achieved at our hospital for ONF [10]. In addition, those results are closely comparable to those reported by Salminen et al. [7] at a university clinic. In their study, the LNFs were performed by a single surgeon, whereas our study included several operating surgeons.

An interesting observation was that fibrin glue seemed to decrease the prevalence of surgical failure statistically. Previously, fibrin glue had been found to be an independent factor in the prevention of failure after LNF [12]. One might assume that anchoring of the fundic wrap would prevent slippage. However, in most of the cases with slippage, fibrin glue was not used, and in only two cases anchoring was not performed. Fibrin glue was mainly placed on serosal folds of the fundic wrap, but it was also put on the lowermost stitch, which anchored the fundic wrap to the gastroesophageal junction. It is likely that this is the most important factor for preventing slippage of the fundic wrap. However, there are probably many different aspects of the surgery that prevent slippage of the fundic wrap, as in one patient with slippage anchoring was used with fibrin glue. These findings support the theoretical basis behind the use of fibrin glue, because it was found to cause scar formation between the serosal folds of a fundic wrap in an experimental animal study [14]. In our previous study the use of fibrin glue was stopped for fear of dysphagia. However, in the presented study postoperative dysphagia was not associated with the use of fibrin glue, which further supports the use of fibrin glue for the prevention of surgical failure after LNF. However, a randomized controlled trial (RCT) should be conducted to further substantiate the assumption.

No differences have been found in the symptomatic outcome between the ONF and LNF groups [5, 7]. Although Salminen et al. [7] found more disruptions of fundoplication wraps in the ONF group, the symptomatic

outcome did not differ between the groups. In our series, no or minimal heartburn was experienced by 90.6 % and no or minimal regurgitation by 95.3 % of the patients. Previously, corresponding percentages of 86.7–97.9 and 94–98.7 % have been reported for heartburn and regurgitation, respectively [5, 6, 15, 16]. In contrast to previous results, dysphagia seemed to be more common in our study group, as 35.9 % of our patients experienced moderate or severe dysphagia. Even though dysphagia is rather common shortly after LNF, the problem has been discovered to resolve in an extended follow-up [5]. Other studies have reported 88–97.9 % of patients having no or occasional dysphagia ten to eleven years after the operation [5, 6, 15, 16]. Dallemagne et al proposed routine gastric fundus mobilization to be related to low dysphagia rates [16]. Furthermore, in Finland, severe dysphagia after LNF occurred only among patients with no fundic mobilization during a ten-year period [17]. Gastric mobilization was performed on only 7.8 % of our patients, and we believe this is the main reason for the higher dysphagia rates in our study. However, RCTs do not support the importance of gastric mobilization in the prevention of dysphagia, suggesting that an experienced laparoscopic surgeon can also achieve good results in regard to postoperative dysphagia without fundic mobilization [18–21]. Even though attempts were made to avoid the effect of the learning curve period, two of the operating surgeons were relatively inexperienced, which may have influenced the results. At present, we divide the 2–3 uppermost short gastric vessels as was recommended in the study by Hunter et al [22]. Moreover, the instrument used to evaluate dysphagia has its limitations with its four-point scale. One may have difficulties in grading the right degree of dysphagia between minimal and moderate, especially if there is a difference between the preoperative and postoperative condition. Only two of the patients characterized their dysphagia as severe, which is in line with the fact that the patient satisfaction is high despite the increase in dysphagia.

Of the unwanted side effects usually related to LNF, flatulence had increased and was moderate or severe in 67.2 % of our patients, whereas bloating had not increased postoperatively (Figs. 5, 6). Other authors have reported the presence of atypical GERD symptoms variedly, but Salminen et al. [7] and Dallemagne et al. [16] also observed increased flatulence after LNF.

The reported rates of using antisecretory medication ten or more years after LNF have ranged from 8.4 to 46.5 % [5–7, 16]. In our series, 9.4 % of patients were on continuous antisecretory medication, and 26.6 % had used medication at some point. There was a correlation between surgical failure and the use of antisecretory medication. Only one patient with surgical failure had not used antisecretory medication. For patients who were on

continuous antireflux medication, surgical failure was found to be 20 times more likely than when medication was not used. However, 17 patients with an intact fundoplication wrap used/had used antisecretory medication. The high rate of postoperative use of antireflux medication is much debated. It has been stated that the drugs are used for the wrong indications [5, 8, 23]. Our questionnaire did not include questions regarding either indications for the use of antisecretory medication or the response of these medicines, which prevented us from further analyzing this subject. One report found that 24 h pH monitoring showed abnormal esophageal acid exposure in only 24 % of the patients who used postoperative acid suppression medication of any kind [8]. Furthermore, at ten years postoperatively, only 35 % of the patients who were dependent on daily PPI therapy due to heartburn and regurgitation showed evidence of reflux pathology in 24 h pH impedance monitoring [5]. Even though it has been demonstrated that the postoperative use of antireflux medication is a poor marker of recurrent reflux, it reflects, to some extent, the overall symptomatic status of patients.

Our results concerning patient satisfaction are quite comparable with prior studies, as 89.1 % of our patients would have opted for surgery again and only 6.3 % would not. Previously, respective percentages of 77.1–93.3 and 5.4–14.6 % have been reported [5–7]. Furthermore, only 6.3 % were dissatisfied with the results, and only two patients felt their preoperative situation had been better.

This study has some obvious limitations. The participation rate was only 59.8 %, which could lead to selection issues. We reviewed the patient records of the non-participating patients, and neither late complications nor reoperations were detected. Because our hospital is the only one in the area performing re-funduplications, it is likely that the patients with major difficulties would have been found. The known demographic characteristics of the non-attending patients are similar to the study population (Table 2), as were the operative techniques used (Table 1), which supports our assumption that there is no selection bias. Another limitation of our study, however, is related to the setting: we did not have preoperative values of symptom scores available to us, and patients therefore had to estimate the preoperative situation retrospectively. This could lead to over- or underestimated values. However, one can assume that the values reflect the overall patient satisfaction and reveal the trend of change reliably. As to the strengths of the present study, we had an independent interviewer who interviewed all the patients, the average follow-up time was extensive, and the fundoplication wraps were evaluated not only by a single researcher but also by the whole team from photographs. Endoscopy has proven a practical method in discovering patients with

defective fundic wraps and patients with recurrent reflux [8, 9, 24].

This study contributes to the previous notion that LNF is associated with fewer surgical failures than ONF. Increased dysphagia and flatulence are the most important side effects of the treatment. The use of technique incorporating the division of short gastric vessels might have led to lower dysphagia rates. Our results indicate that LNF can well be performed in a community-based hospital with acceptable long-term results.

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References

- Galmiche JP, Hatlebakk J, Attwood S et al (2011) Laparoscopic antireflux surgery versus esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 305:1969–1977
- Chang EY, Morris CD, Seltman AK et al (2007) The effect of antireflux surgery on esophageal carcinogenesis in patients with barrett esophagus: a systematic review. *Ann Surg* 246:11–21
- Gatenby PA, Ramus JR, Caygill CP et al (2009) Treatment modalities and risk of development of dysplasia and adenocarcinoma in columnar-lined esophagus. *Dis Esophagus* 22:133–142
- Lagergren J, Bergström R, Lindgren A et al (1999) Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 340:825–831
- Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al (2009) Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. *Ann Surg* 250:698–706
- Morgenthal CB, Shane MD, Stival A (2007) The durability of laparoscopic Nissen fundoplication: 11-year outcomes. *J Gastrointest Surg* 11:693–700
- Salminen P, Hurme S, Ovaska J (2012) Fifteen-year outcome of laparoscopic and open Nissen fundoplication: a randomized clinical trial. *Ann Thorac Surg* 93:228–233
- Lord RV, Kaminski A, Öberg S et al (2002) Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. *J Gastrointest Surg* 6:3–10
- Luostarinen M (1993) Nissen fundoplication for reflux esophagitis. Long-term clinical and endoscopic results in 109 of 127 consecutive patients. *Ann Surg* 217:329–337
- Rantanen TK, Halme TV, Luostarinen ME et al (1999) The long term results of open antireflux surgery in a community-based health care center. *Am J Gastroenterol* 94:1777–1781
- Salminen PT, Hiekkänen HL, Rantala AP et al (2007) Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. *Ann Surg* 246:201–206
- Rantanen T, Neuvonen P, Iivonen M et al (2011) The impact of fibrin glue in the prevention of failure after Nissen fundoplication. *Scand J Surg* 100:181–185
- Demeester TR, Johnson LF, Joseph GJ et al (1976) Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 184:459–470
- Isolauri J, Viljakka M, Helin H et al (1997) Disruption of experimental fundic folds is prevented by interserosal scarring. *Br J Surg* 84:548–550

15. Fein M, Bueter M, Thalheimer A et al (2008) Ten-year outcome of laparoscopic antireflux surgery. *J Gastrointest Surg* 12:1893–1899
16. Dallemagne B, Weerts J, Markiewicz S et al (2006) Clinical results of laparoscopic fundoplication at ten years after surgery. *Surg Endosc* 20:159–165
17. Rantanen TK, Oksala NK, Oksala AK et al (2008) Complications in antireflux surgery: national-based analysis of laparoscopic and open fundoplications. *Arch Surg* 143:359–365
18. O'Boyle CJ, Watson DI, Jamieson GG et al (2002) Division of short gastric vessels at laparoscopic nissen fundoplication: a prospective double-blind randomized trial with 5-year follow-up. *Ann Surg* 235:165–170
19. Chrysos E, Tzortzinis A, Tsiaoussis J et al (2001) Prospective randomized trial comparing Nissen to Nissen-Rossetti technique for laparoscopic fundoplication. *Am J Surg* 182:215–221
20. Luostarinen ME, Isolauri JO (1999) Randomized trial to study the effect of fundic mobilization on long-term results of Nissen fundoplication. *Br J Surg* 86:614–618
21. Watson DI, Pike GK, Baigrie RJ et al (1997) Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg* 226:642–652
22. Hunter JG, Smith CD, Branum GD et al (1999) Laparoscopic fundoplication failures: patterns of failure and response to fundoplication revision. *Ann Surg* 230:595–604
23. Bammer T, Hinder RA, Klaus A et al (2001) Five- to eight-year outcome of the first laparoscopic Nissen fundoplications. *J Gastrointest Surg* 5:42–48
24. O'Hanrahan Marples M, Bancewicz J (1990) Recurrent reflux and wrap disruption after Nissen fundoplication: detection, incidence and timing. *Br J Surg* 77:545–547

Does Nissen Fundoplication Provide Lifelong Reflux Control? Symptomatic Outcome After 31–33 Years

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Abstract

Background A substantial number of people are suffering from gastroesophageal reflux disease (GERD). The indication for surgical treatment is the failure of medical treatment in patients with objectively verified GERD. The use of PPIs has been noted to increase with the length of follow-up after fundoplication, raising questions concerning the durability of surgical results. The aim of the study was to investigate the results of open Nissen fundoplication (ONF) over a follow-up of more than 31 years.

Methods ONF was performed for 38 consecutive patients. Questionnaires concerning long-term outcome were sent on December 14, 2015, to the 24 patients still living. Long-term symptom evaluation was carried out using the Gastrointestinal Symptom Rating Scale (GSRS), Visick grading, a Visual Analog Scale (VAS), the DeMeester–Johnson reflux scale, and the 15D tool.

Results Seventeen (70.8%) of the 24 patients still living participated in the study. The typical symptoms of GERD had resolved significantly. Dysphagia was graded as none or minimal by 13 (81.3%) patients. The mean 15D score of the patient group was clinically and statistically the same (0.896 vs. 0.899) as that of the age- and sex-standardized general population ($p = 0.912$). Six (15.8%) patients had used antireflux medication after the operation and 4 of them (10.6%) continuously.

Conclusions Patients in the present study used PPIs less frequently than what has been reported in previous long-term follow-up studies. Our results indicate that successful surgery may provide lifelong relief of GERD symptoms and normalize the health-related quality of life in GERD patients.

Introduction

A substantial number of people are suffering from gastroesophageal reflux disease (GERD), as the condition has become the most prevalent gastrointestinal disorder in the

Western countries. The prevalence of weekly heartburn and/or regurgitation is 9.8–27.8%, and 32–66% of people report monthly or annual symptoms [1–3]. The burden of the disease on healthcare resources is notable [4].

Medical and surgical treatments have proven equally effective in the treatment of patients with GERD initially responsive to proton pump inhibitors (PPIs) [5]. Because of the side effects related to surgical treatment, however, most patients are treated medically.

The indication for surgical treatment is the failure of medical treatment in patients with objectively verified GERD [6]. As approximately 30% of heartburn patients experience at least weekly breakthrough symptoms despite

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the use of PPIs and 35.4% are not unequivocally satisfied with the medication, there is a demand for surgical treatment for carefully selected patients [7]. Providing the patients adequate information about the benefits and harms is essential for successful surgery.

Even though the first Nissen fundoplication was performed 60 years ago [8], the longest follow-up series are currently limited to 20 years [9, 10]. The number of defective wraps and the use of PPIs have been noted to increase with the length of follow-up after fundoplication, raising questions concerning the durability of the surgical results [10–14]. As the surgical treatment irreversibly alters the anatomy of the cardia region, it is of major interest to understand how effective the procedure is providing life-long reflux control. The aim of the present study was to determine the results of open Nissen fundoplication (ONF) over a follow-up of more than 31 years.

Methods

Patients

ONF was performed for 38 consecutive patients (20 females, mean age at the operation 44 years, range 23–60) between January 7, 1983, and November 6, 1984, at Tampere University Hospital. The indications were either erosive esophagitis with (5 patients) or without (17 patients) GERD symptoms, or refractory GERD symptoms despite H₂ blocker therapy (16 patients). Preoperative

evaluation included upper gastrointestinal endoscopy in all cases, esophageal pH monitoring in 8 cases (spontaneous gastroesophageal reflux detected in all cases), and the Bernstein test in 1 (positive) case. The endoscopic findings were graded according to the Savary–Miller classification as: grade II 20 and grade IV 3 (Barrett's esophagus in one preoperative endoscopy) [15]. Fourteen patients (36.8%) had died during the follow-up of causes unrelated to GERD (Table 1), and seven (18.4%) patients did not participate in the long-term follow-up study. The indications, as divided for the participating, the non-participating, and the deceased patients, are described in Table 2.

Surgical procedure

All of the operations were performed by an experienced surgeon (M.M.). Open anterior Nissen-Rossetti fundoplication was carried out through a midline incision. Fundic mobilization was done only selectively in order to achieve a loose enough wrap. Three non-absorbable stitches were used to construct a 2- to 3-cm-long fundic wrap. The wrap was anchored to the gastroesophageal junction with the lowermost stitch. Hiatal closure was not done. A 32-French nasogastric tube was inserted into the esophagus during the creation of the fundic wrap. In two patients, perioperative esophageal dilatation was achieved using an Eder-Puestow dilatator due to esophageal stricture. Additional cholecystectomy was performed for two patients because of symptomatic gallstones.

Data collection

Preoperative and short-term postoperative data were collected prospectively by one of the authors (M.M.). For the long-term follow-up results, another author (T.R.) retrospectively reviewed all the patient documents on December 7, 2015. All possibly related procedures (endoscopies, reoperations due to GERD or related to the wound) were noted. Death certificates for the deceased patients were requested from Statistics Finland to ascertain the final causes of death. The questionnaires concerning long-term outcomes were sent on December 14, 2015, to the 24 patients still living. The questionnaires were resent a further two times to those patients who did not respond. In all

Table 1 Causes of death among the 14 deceased patients

Cause of death	Number of patients
Myocardial infarction	4
Malignancy	4*
Vascular dementia	2
Alcohol intoxication	1
Meningitis (alcoholic)	1
Pneumonia	1
Suicide	1

* No cancer in the gastrointestinal tract

Table 2 Indications for operation

Indication	Attending patients	Non-attending patients	Deceased patients
Erosive reflux disease (%)	58.8	57.1	57.1
Positive pH or Bernstein test (%)	11.8	28.6	21.4
Heartburn and regurgitation, and hiatus hernia or Barrett's esophagus (%)	29.4	14.3	21.4

of the questionnaires, the patients were requested to define both the preoperative and the present situations.

Long-term symptom evaluation was made using the Gastrointestinal Symptom Rating Scale (GSRS) [16], Visick grading [17], a Visual Analog Scale (VAS; bloating and flatus) [18], and the DeMeester-Johnson reflux scale (heartburn, regurgitation, dysphagia) [19]. When analyzing the VAS results, a score of 0 was considered as having no symptoms while 100 represented the worst possible symptoms. To simplify the comparison, the VAS values were later converted to represent a four-point symptom severity scale as follows: 0 = none, 1–33 = minimal, 34–66 = moderate, and 67–100 = severe. New-onset symptoms after the operation were inquired about.

Health-related quality of life was defined using the 15D tool [20]. A comparison between the 15D results of our patient group and a general Finnish population was conducted (age- and sex-standardized general population $n = 2213$) [21]. In addition, the patients were requested to state their satisfaction level with the results of the surgery (satisfied, undecided, or unsatisfied). They were also asked whether they would still prefer surgical treatment over medical treatment if they were to have the same kind of symptoms as preoperatively.

Finally, patients were asked about the possible postoperative use of acid-suppressing drugs and further operative procedures (reoperations, upper gastrointestinal endoscopies, and dilatations).

Statistical analysis

The statistical significance between pre- and postoperative values concerning heartburn, regurgitation, dysphagia, and Visick grading was calculated with a marginal homogeneity test. A pairwise *T* test was used to evaluate GSRS and 15D mean values. The Wilcoxon test was applied to assess the VAS data. The values of the 15D data were analyzed with the Mann–Whitney *U* test. *P* values less than 0.05 were considered significant.

Ethics

This study was approved by the Ethical Committee of Kuopio University Hospital.

Results

Short-term recovery

During the initial recovery, one patient had a wound infection, which resolved with antibiotics and caused no long-term sequelae. For 35 patients (17 attending, 6 non-

attending, and 12 deceased patients), surveys concerning symptom control and satisfaction were carried out 3–6 months after the operation. According to the short-term results, three patients (8.6%) had mild heartburn, and five patients (14.3%) had mild dysphagia, while the others reported no heartburn or dysphagia. Twenty-seven patients evaluated the results of the surgery with a Visick grade of 1 (77.1%), and 8 scored the results as grade 2 (22.9%). Sixteen (45.7%) patients were satisfied and 19 (54.3%) highly satisfied with the results. At this point, 4 upper gastrointestinal endoscopies were performed due to mild heartburn (3 patients) or mild dysphagia (1 patient). The endoscopies revealed normal fundic wraps with no esophagitis in all cases.

After a mean follow-up of 27 months, 19 patients (10 attending, 3 non-attending, and 6 deceased patients) were evaluated again. None of the 19 patients had reflux symptoms, but one had mild dysphagia. Eighteen patients (94.7%) gave the result a Visick grade of 1 and one patient a (5.3%) grade 2. All the patients were satisfied with the operative results.

Long-term results

Sixteen of the 24 patients (66.7%) responded to all of the questionnaires concerning the long-term results, while one patient completed only the GSRS questionnaire and answered the questions regarding satisfaction with the results of surgery. Therefore, 17 of the 24 still living patients (70.8%) participated in the long-term follow-up. The patient characteristics of the attending, the non-attending, and the deceased patients are described in Table 3.

The mean age of the participating patients at the time of the operation was 43.4 years (range 30–59 years) and, after the mean follow-up of 32.0 years (range 31.3–33.0 years), 69.5 years (range 61–87 years).

After combining the results of the survey and the data from the patient records, we found that four out of 38 patients (10.6%) had been on continuous antireflux medication (three patients used PPIs and one patient H2 blockers) and two had used occasional medication (one patient used PPIs and the other alginate). Therefore, six (15.8%) patients had used antireflux medication after the operation. Four of these were attending patients (23.5%), and 2 were deceased (14.3%) patients. Two patients used the medication for heartburn (1 attending and 1 deceased patient; PPIs), two (both attending patients) for upper abdominal pain (H2 blocker + alginate), and two (1 attending and 1 deceased patient) because of the use of NSAIDs (PPIs).

One patient who did not participate in the study had undergone a correction of an incisional hernia (2.6%). By the end of our long-term follow-up period, upper

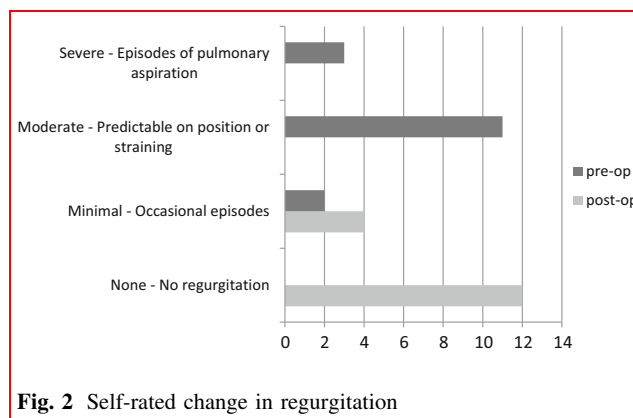
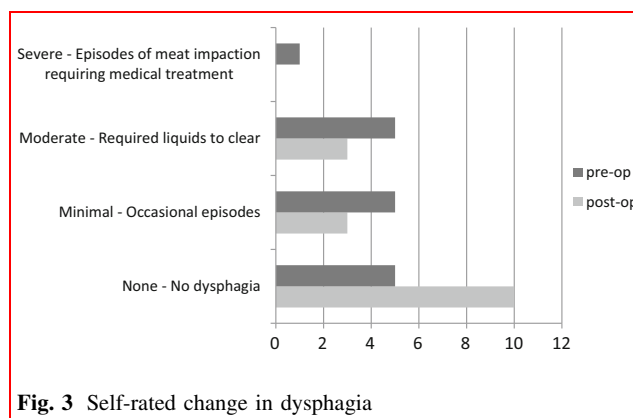
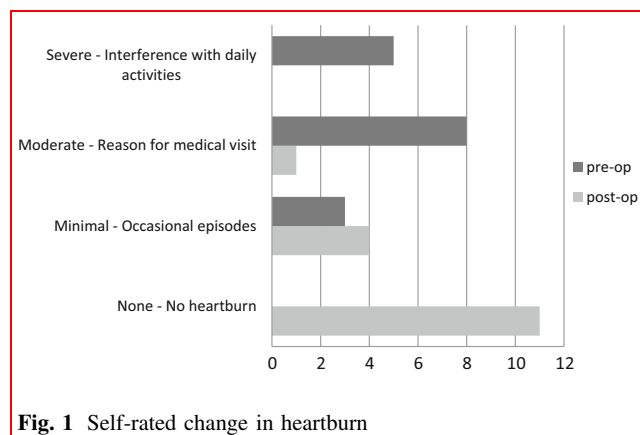
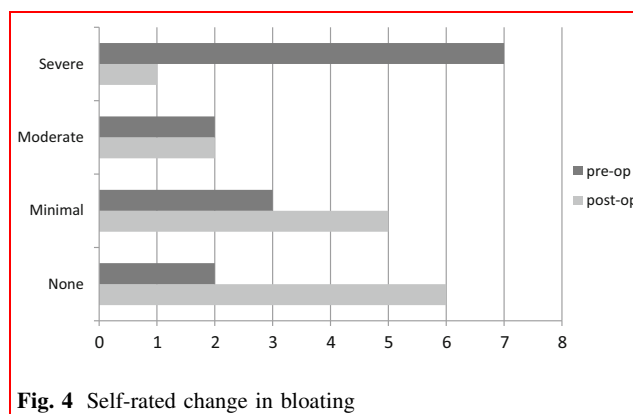
Table 3 Patient characteristics

Characteristics	Attending patients (<i>n</i> = 17)	Non-attending patients (<i>n</i> = 7)	Deceased patients (<i>n</i> = 14)	The whole study population (<i>n</i> = 38)
Male sex (%)	47.1	57.1	50.0	50.0
Mean age at operation (years)	43.4	34.4	49.9	44.2
Diagnosis of Barrett's esophagus (%)	11.8	0.0	7.1	7.9
Postoperative use of antireflux medication (%)	23.5	0.0	14.3	15.8

gastrointestinal endoscopy had been performed on 7 patients (5 attending and 2 deceased patients); on 3 patients several times due to surveillance of Barrett's esophagus (Fundic wrap was normal in all cases); and on another 3 due to an unknown reason (fundic wrap was normal in each case). In one of the deceased patients (2.6%), a disruption of the wrap, recurrent hiatal hernia, and esophagitis had been discovered in an endoscopy, which was done because of GERD symptoms. The patient was managed conservatively with pantoprazole 40 mg once daily. Neither dilatations nor reoperations due to recurrent GERD had been performed. In addition, no other visits to our hospital due to GERD were found.

The results of our questionnaire revealed that the typical GERD symptoms had resolved significantly, as 15 (93.8%) patients experienced either no or only minimal heartburn ($p < 0.001$) (Fig. 1), and 12 patients (75%) had no regurgitation, while the remaining four (25.0%) graded their regurgitation as minimal ($p < 0.001$) (Fig. 2). Dysphagia was graded as none by ten (62.5%), minimal by three (18.8%), and moderate by three (18.8%) patients ($p = 0.013$) (Fig. 3).

Six (37.5%) patients reported no bloating, five (31.3%) had minimal bloating, two (12.5%) had moderate bloating, and one (6.3%) patient had severe bloating ($p = 0.009$) (Fig. 4). Two (12.5%) patients were undecided. Four (25.0%) patients reported no flatulence, seven had minimal flatulence (43.8%), and three (18.8%) had moderate

**Fig. 2** Self-rated change in regurgitation**Fig. 3** Self-rated change in dysphagia**Fig. 1** Self-rated change in heartburn**Fig. 4** Self-rated change in bloating

flatulence ($p = 0.12$) (Fig. 5). As with bloating, two (12.5%) patients were undecided concerning flatulence. One person felt the bloating was worse postoperatively (VAS 50) than preoperatively (VAS 30), and another scored VAS 80 for both pre- and postoperative values. Two persons felt their flatulence had become more prominent postoperatively, another two observed no difference, and the rest felt the preoperative situation was worse.

The mean Visick grade was 3.94 preoperatively and 0.625 after the follow-up ($p < 0.001$). The mean GSRS score decreased from 31.3 to 7.9 ($p < 0.001$).

The mean 15D score of the patient group was clinically and statistically the same (0.896 vs. 0.899) as that of the age- and sex-standardized general population ($p = 0.912$). The only dimension with a statistically significant difference was mental function, the scores of which were 0.96 for the patient group and 0.86 for the general population ($p = 0.008$) (Fig. 6).

Overall, 94.1% of the patients were satisfied with the results of surgery, while one patient graded the satisfaction level undecided because of flatulence and inability to vomit. There were no unsatisfied patients, and all of the patients would have chosen to undergo the surgery again if

they were to have the same kind of symptoms as preoperatively—even the one grading the satisfaction level as undecided.

Discussion

In our study, we found the subjective reflux control of our patient group to still be surprisingly good more than 30 years after the ONF, and more importantly, the health-related quality of life was the same as that of the general population. To our knowledge, this study provides the longest follow-up period published after fundoplication.

After the introduction of laparoscopic Nissen fundoplication (LNF) in the 1990s, the number of antireflux procedures rose rapidly but has since declined closer to the numbers of the pre-laparoscopic era [22–24]. One of our interests was to review the indications for surgical treatment in the 1980s. Twenty-two patients in the present study were operated on for severe GERD with erosive esophagitis verified in preoperative endoscopy, but 16 were operated on because of H2-blocker-resistant symptoms. pH monitoring was done for only eight patients, which reflects the routine clinical practice of that time, as the availability of objective testing was limited. Roughly speaking, the indications can be considered similar to those we found in the laparoscopic era [23]. It can be speculated that the less invasive nature of LNF probably made it a more liberally offered treatment than open surgery, leading to the increase in antireflux surgery in the 1990s.

According to patient-reported results, fundoplication offers durable symptom control more than 30 years after the operation. In our study, 93.8% of the patients had no or minimal heartburn, and the results concerning regurgitation were even better as there were no patients grading their regurgitation as moderate or severe. In other long-term follow-up studies, 76–91% and 82–91% of patients have had no or only minimal heartburn and regurgitation, respectively, after ONF [9, 13, 25, 26]. The long-term symptomatic outcome has been proven to be similar after LNF and ONF [11, 13].

Of the treatment-related side effects, the dysphagia rate was comparable to other studies, as 18.8% reported moderate dysphagia, but no severe dysphagia was found [9, 11, 13, 26]. The rates for bloating and flatulence were somewhat lower than those reported in previous long-term follow-up studies [11, 25, 26], and in fact, these symptoms were graded as lower after the follow-up than preoperatively. Still, flatulence was named as a new-onset symptom on three occasions, an inability to belch or vomit twice, constipation also twice, and bloating once after the operation. Overall, only five patients reported new-onset symptoms. A retrospective evaluation of the preoperative

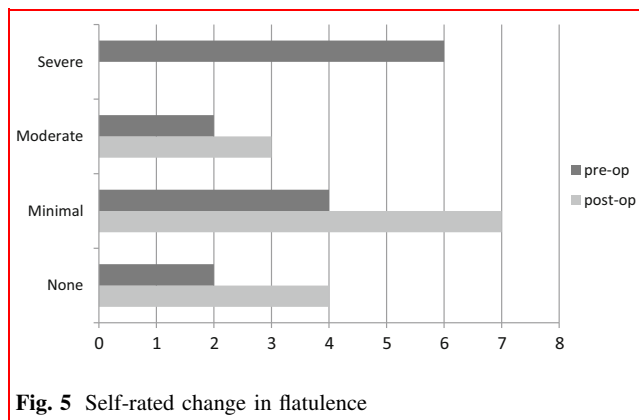


Fig. 5 Self-rated change in flatulence

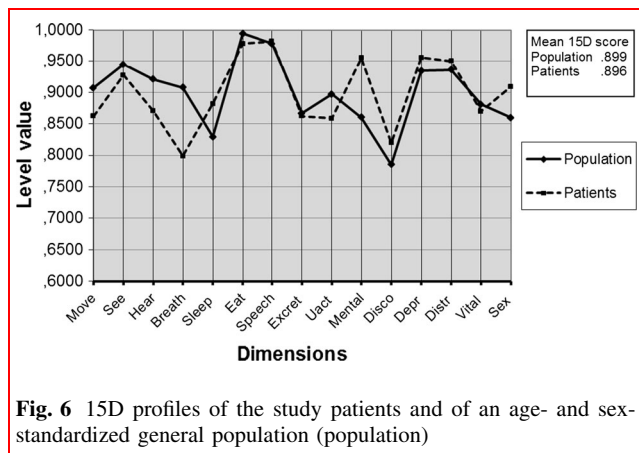


Fig. 6 15D profiles of the study patients and of an age- and sex-standardized general population (population)

state of these symptoms is not ideal, but one can assume the majority of the patients are not disturbed by the treatment-related side effects more than 30 years postoperatively.

In a Danish population-based study, the 15-year cumulative risk of long-term PPI use was 56.6% after antireflux surgery [14]. Salminen et al. [11] found that 15.1% of patients used daily PPIs 15 years after fundoplication and 46.5% had used PPIs overall. In the study by Broeders et al. [13] the daily PPI use was 22.4% at 9.8 years after ONF. The figures in our patient group compare favorably to those previously described, as the overall use of antireflux medication was 15.8, and 10.6% of the patients had been on continuous medication. Furthermore, only two (2/38, 5.3%) patients had been on continuous PPI treatment because of heartburn. According to these results, the need for antireflux medication may not necessarily explode with the length of follow-up.

GERD has been verified to lower the health-related quality of life [27]. One of the most important results of this study is the fact that the health-related quality of life of the patient group was similar to that of the general population. In our previous study, we found that dissatisfaction with the treatment lowered the 15D scores, while the scores of the satisfied patients were clinically the same as those of the general population [28]. The results of this study are in line with our previous results, since satisfaction with the treatment in this patient group proved to be high. There are only few previously published studies using generic multidimensional health-related quality of life instruments after fundoplication.

Our study has some limitations. First of all, the size of our patient group is relatively small. Also, the high number of deceased patients at the end of follow-up and an only fair participation rate increase the risk of selection bias. In addition, it can be speculated that the healthiest live the longest, which might further misrepresent the results to seem better, at least as far as the quality of life is concerned. However, to enhance the reliability of the study, we went through the patient records of the whole patient group, and it is reasonable to assume that the persisting problems and complications concerning GERD among the non-attending were found. In addition, our hospital is the only center in this area in which reoperations and dilations are performed, and therefore, all severe problems would have been seen when the patient records were analyzed. Also, only one patient had moved outside the referral area of our hospital, and this patient also attended the study. Another limitation of our study is the lack of objective results. Previously, heartburn and regurgitation, postoperative use of antireflux medication, and dissatisfaction with the treatment have been found to be associated with defective fundic wraps [9, 11, 29]. The good results of

this study indirectly implicate durable surgical outcomes in our follow-up group.

The results of this study concerning typical reflux symptoms, patient satisfaction, as well as postoperative PPI use are surprisingly good in comparison with previous long-term studies. In part, the good results may stem from issues in participation or in the study setting—only one patient was not completely satisfied with the results. However, it is also possible that the final selection of patients for surgical treatment may have succeeded exceptionally well, thus leading to good results. The fact that the patients were operated on before the introduction of PPIs may also have given the patients a strong subjective experience of the power of surgical treatment compared to the conservative treatment available in the 1980s. The long-term results of this study do not represent the long-term results of antireflux surgery in general, but rather provide an idea of the outcomes in cases of successful ONF.

In conclusion, against our primary hypothesis, patients in the present study used PPIs less frequently than what has been reported in previous long-term follow-up studies. Therefore, our results indicate that successful surgery may provide lifelong relief of reflux symptoms and normalize the health-related quality of life in GERD patients.

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Compliance with ethical standards

Conflict of interest None.

References

1. Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E et al (2004) Symptoms of gastro-oesophageal reflux: prevalence, severity, duration and associated factors in a Spanish population. *Aliment Pharmacol Ther* 19:95–105
2. El-Serag HB, Petersen NJ, Carter J et al (2004) Gastroesophageal reflux among different racial groups in the United States. *Gastroenterology* 126:1692–1699
3. Ronkainen J, Aro P, Storskrubb T et al (2005) High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 40:275–285
4. Peery AF, Crockett SD, Barritt AS, et al (2015) Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology*. 149:1731, 1741.e3
5. Galmiche J, Hatlebakk J, Attwood S et al (2011) Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. *JAMA* 305:1969–1977
6. Kahrilas PJ, Shaheen NJ, Vaezi MF et al (2008) American Gastroenterological Association Medical Position Statement on

- the management of gastroesophageal reflux disease. *Gastroenterology* 135:1383–1391
7. Chey WD, Mody RR, Izat E (2010) Patient and physician satisfaction with proton pump inhibitors (PPIs): are there opportunities for improvement? *Dig Dis Sci* 55:3415–3422
 8. Nissen R (1956) Eine einfache Operation zur Beeinflussung der Refluxoesophagitis. *Schweizerische medizinische Wochenschrift* 86:590–592
 9. Luostarinen M, Isolauri J, Laitinen J et al (1993) Fate of Nissen fundoplication after 20 years. A clinical, endoscopical, and functional analysis. *Gut* 34:1015–1020
 10. Robinson B, Dunst CM, Cassera MA et al (2015) 20 years later: laparoscopic fundoplication durability. *Surg Endosc* 29:2520–2524
 11. Salminen P, Hurme S, Ovaska J (2012) Fifteen-year outcome of laparoscopic and open Nissen fundoplication: a randomized clinical trial. *Ann Thorac Surg* 93:228–233
 12. Luostarinen M (1993) Nissen fundoplication for reflux esophagitis. Long-term clinical and endoscopic results in 109 of 127 consecutive patients. *Ann Surg* 217:329–337
 13. Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al (2009) Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. *Ann Surg* 250:698–706
 14. Lodrup A, Pottegard A, Hallas J et al (2014) Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study. *Gut* 63:1544–1549
 15. Savary M, Miller G (1977) *Der Ösophagus. Lehrbuch und endoskopischer Atlas*. Gassmann, Solothurn
 16. Revicki DA, Wood M, Wiklund I et al (1998) Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. *Qual Life Res* 7:75–83
 17. VISICK AH (1948) Measured radical gastrectomy; review of 505 operations for peptic ulcer. *Lancet. passim*; 1(6501):505
 18. Reading A (1989) Testing pain mechanisms in persons in pain. In: Wall P, Melzack R (eds) *Textbook of pain*, 2nd edn. New York, Churchill Livingstone Inc, pp 269–280
 19. Demeester TR, Johnson LF, Joseph GJ et al (1976) Patterns of gastroesophageal reflux in health and disease. *Ann Surg* 184:459–470
 20. Sintonen H (2001) The 15D instrument of health-related quality of life: properties and applications. *Ann Med* 33:328–336
 21. Koskinen S, Lundqvist A, Ristiluoma N. Health, functional capacity and welfare in Finland in 2011. Helsinki: National Institute for Health and Welfare (THL); 2012. Report No.: 68/2012
 22. Finks JF, Wei Y, Birkmeyer JD (2006) The rise and fall of antireflux surgery in the United States. *Surg Endosc* 20:1698–1701
 23. Rantanen T, Neuvonen P, Iivonen M et al (2011) The impact of fibrin glue in the prevention of failure after Nissen fundoplication. *Scand J Surg SJS* 100:181–185
 24. Rantanen TK, Oksala NKJ, Oksala AK et al (2008) Complications in antireflux surgery: national-based analysis of laparoscopic and open fundoplications. *Arch Surg; discussion* 365;143:359–365
 25. Mardani J, Lundell L, Engstrom C (2011) Total or posterior partial fundoplication in the treatment of GERD: results of a randomized trial after 2 decades of follow-up. *Ann Surg* 253:875–878
 26. Lundell L, Miettinen P, Myrvold HE et al (2009) Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clin Gastroenterol Hepatol. quiz* 1260;7:1292–1298
 27. Kamolz T, Pointner R, Velanovich V (2003) The impact of gastroesophageal reflux disease on quality of life. *Surg Endosc* 17:1193–1199
 28. Neuvonen P, Iivonen M, Sintonen H et al (2014) Health-related quality of life 10 years after laparoscopic nissen fundoplication—results of a community-based hospital. *J Laparoendosc Adv Surg Tech Part A* 24:134–138
 29. Neuvonen P, Iivonen M, Rantanen T (2014) Endoscopic evaluation of laparoscopic nissen fundoplication: 89% success rate 10 years after surgery. *World J Surg* 38:882–889. doi:[10.1007/s00268-013-2349-2](https://doi.org/10.1007/s00268-013-2349-2)