

## Results in Antireflux Surgery, an Analysis of Case-Controlled Cohorts versus Multicenter Studies and Meta-Analyses

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### Rezumat

*Rezultate în chirurgia antireflux, o analiză a seriilor de cazuri controlate versus studii multicentrice și meta-analize*

**Introducere:** Odată cu apariția tehnicilor minim invazive, fundoplicatura laparoscopică Nissen și fundoplicatura parțială Toupet au avut mare succes în managementul BRGE. În ultimii 10 ani, o serie de tehnici noi, foarte atractive pentru tratamentul BRGE au intrat pe piață. Aceste tehnici includ gastroplicatura transorală, alte tipuri de plicaturi endoscopice și implantarea unui dispozitiv magnetic la nivel sfincterian [*magnetic sphincter augmentation (MSA)*]. Aceste noi tehnologii sunt promovate excesiv de companiile respective, pe baza faptului că ar produce mai puține efecte secundare. Scopul acestui articol este de a prezenta ratele de succes ale noilor tehnici aplicate în tratamentul BRGE.

**Metode:** Acest articol analizează literatura de specialitate pe tema fundoplicaturii laparoscopice (FL), a fundoplicaturii transorale fără incizie (TIF) și a MSA laparoscopice. Studiile incluse au fost clasificate în funcție de tipul lor în 2 grupuri: grupul 1 conține serii de cazuri controlate mari sau studii comparative (n > 100 de cazuri) din centre cu volum mare, iar grupul 2 include studii ce compară diferite tehnologii utilizate în procedurile antireflux, studii multicentrice și meta-analize ale studiilor despre BRGE.

**Rezultate:** În total, 4030 de rezumate au fost analizate în funcție de cuvintele cheie selectate. După criteriile de excludere, au fost selectate și analizate 19 publicații. În ceea ce privește grupul 1 și FL (2565 pacienți), morbiditatea a variat între 2,0-4,8 % din cazuri. Perioada de urmărire a fost cuprinsă între 36 și 222 luni, iar majoritatea acestor pacienți au fost urmăriți > 5 ani. În grupul 2,

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peste 150 de studii și o serie de registre multicentrice au fost rezumate în aceste 9 publicații selectate. Perioadele de urmărire au fost substanțial mai scurte, fiind cuprinse între 7 și 48 de luni. **Concluzii:** Se poate afirma că managementul pacientului în centrele cu volum mare și experiență vastă în utilizarea acestor tehnologii pot contribui substanțial la rezultate excelente pentru mai multe tehnici anti-reflux, care pot atinge un nivel de calitate peste rezultatele registrelor și meta-analizelor.

**Cuvinte cheie:** BRGE, chirurgie antireflux, fundoplicatura laparoscopică, fundoplicatura laparoscopică Nissen, fundoplicatura laparoscopică Toupet, proceduri endoscopice antireflux, magnetic Sphincter augmentation, Linx

## Abstract

**Introduction:** With the advent of minimally invasive techniques, laparoscopic Nissen fundoplication and Toupet partial fundoplication have been very successful in the management of GERD. In the past 10 years, a number of very attractive new technologies have entered the market around therapeutic GERD-management such as Transoral Incisionless Gastroplication, other endoscopic plication techniques, and the implantation of the magnetic sphincter augmentation (MSA). These new technologies are excessively promoted by the respective companies, propagating their techniques as causing fewer side effects. The purpose of this paper is an overview on the success-rates of these differently used techniques and technologies and, in addition, different study-designs.

**Methods:** A literature review was performed searching for publications on laparoscopic fundoplication (LF), Transoral Incisionless Fundoplication (TIF), and laparoscopic MSA. The reported classified were separated according to their design into (group 1) large case-controlled series or comparative studies (n > 100 cases) from high-volume centers and into (group 2) trials between different technologies of antireflux procedures, multicenter-studies, and meta-analyses of GERD-trials.

**Results:** In total, 4030 abstract were screened according to the selected key words. Following the section criteria, 19 publications were selected and analyzed. Regarding group 1 and LF (selected studies 2565 patients), the morbidity ranged from 2.0-4.8 % of cases. With a follow-up time of 36-222 months most of these patients were followed > 5 years. In group 2, more than 150 studies and several multicenter-registries were summarized in these 9 selected publications. The overall follow-up periods were substantially shorter with a range of 7-48 months.

**Conclusions:** It can be concluded that special efforts in patient management in high volume centers and a vast experience may substantially contribute to excellent results for several antireflux techniques, which may reach a level of quality above results of registries and meta-analyses.

**Key words:** GERD, antireflux surgery, laparoscopic fundoplication, laparoscopic Nissen fundoplication, laparoscopic Toupet fundoplication, endoscopic antireflux procedures, magnetic Sphincter augmentation, Linx

## Introduction

Therapeutic management of Gastroesophageal Reflux Disease (GERD) is a matter of discussion between several subspecialties, mainly gastroenterologists and surgeons (1-4). Since

1956, the principle of fundoplication by mechanical enforcement of the weakened antireflux barrier has been used with varying success (5,6). A major problem around this therapeutic principle emerged very early regarding postoperative dysphagia and other

side-effects such as early satiety, vomiting, increased flatulence, and diarrhea (7). The latter problems led to a first wave of criticism of the fundoplication technique especially in the gastroenterologic arena, because they usually had to treat patients with fundoplication failures and severe restrictions in quality of life.

Technical modifications of the fundoplication technique helped somewhat. One alternative was the step towards partial fundoplications with potentially fewer severe side-effects (6,7). Another technical alternative was the modification of the Nissen-wrap by shortening the fundoplication and creating a floppy version, using a large 54-60 French bougie for cardia calibration, which was very helpful, however, rarely followed by surgeons (8,9).

With the advent of minimally invasive techniques, laparoscopic Nissen fundoplication and Toupet partial fundoplication have been very successful in the management of GERD, since the early reconvalescence and limited postoperative pain and complications led to a "boom" for these operations (10-14). However, the broad application of laparoscopic surgery also in rather inexperienced surgical centers led to the fact that every general surgeon applied this technique in many patients. In a second wave of problems, patient selection, indications for surgical treatment of GERD and necessary adherence to technical necessities were not followed as necessary, resulting again in unfavorable results for laparoscopic fundoplication (15).

This paved the way for the introduction of alternative technologies associated with flexible endoscopic techniques such as endoscopic suturing and implants (16,17). However, the insufficient durability and technical short-comings of the latter techniques limited their success (16-19).

In the past 10 years, a number of very attractive new technologies have entered the market around therapeutic GERD-management such as Transoral Incisionless Gastroplication, other endoscopic plication techniques and the implantation of the magnetic sphincter augmentation (MSA) by the LINX™-device (20-

24). These new technologies are excessively promoted by the respective companies, propagating their techniques as causing fewer side effects while being promoted as highly successful in GERD-therapy (24-26). These marketing efforts usually used the devastating results of some publications about fundoplication in widely criticizing the principle of laparoscopic fundoplication as such (27-30).

Despite this development, laparoscopic fundoplication (LF) is still the most frequently used procedure for the interventional treatment of GERD especially in esophageal centers around the world (31-33). In addition, there is a large variety of reported success-rates among the GERD literature from meta-analyses and multi-center studies, comparative studies between new-technology-studies and traditional laparoscopic fundoplication as well as large case-controlled studies from experienced high-volume esophageal centers (3,31-36).

The purpose of this manuscript is an overview on the success-rates of these differently applied techniques and technologies in interventional endoscopic and laparoscopic therapy for GERD. It was important to verify and demonstrate the differences in the results of various study designs and the discussion and interpretation of these results.

## Methods

A literature review was performed searching for publications on laparoscopic fundoplication, endoscopic antireflux procedures (EAP) mainly Transoral Incisionless Fundoplication (TIF), and laparoscopic MSA to select the main procedures on the current market. The reported studies were categorized according to their design into (group 1) large case-controlled series or comparative studies ( $n > 100$  cases) from high-volume centers (reports from  $>500$  documented patients available in literature) and into (group 2) trials between different technologies of antireflux procedures, multicenter-studies, and meta-analyses of therapeutic GERD-trials.

For the retrieval of the published literature, the following terms were entered in the

pubmed database: laparoscopic fundoplication; transoral incisionless fundoplication; magnetic sphincter augmentation, endoscopic antireflux procedures.

The published studies were retrieved from “pubmed.gov” from the past 6 years and were afterwards selected by the authors in order to gain the most recent evidence on the subject. In a subsequent conference, occurring discrepancies in selection were discussed and a unanimous decision was established for the final selection to enter the analysis.

The selected manuscripts were analyzed according to the following parameters: first author and year of publication, the number of patients treated (n), the morbidity of the procedure in %, the mean length of follow-up time in months, if available, also the percentage of followed patients compared to the initial treated cohort, the percentage of good to excellent results of the treated patients, more in detail the percentage of patients in follow-up with

persistent dysphagia, the percentage of patients with reflux recurrence if available either based on pH-monitoring data, presence of esophagitis and/ or presence of postoperative heartburn and regurgitation as well as the rate of necessary redo-surgery among the published cohort over the follow-up time.

The results were summarized in tables and a conference call on the interpretation of these results was arranged among the authors and documented.

## Results

In total, 4030 abstract were screened according to the selected key words. Following the section criteria, 19 publications were selected and analyzed (33,37-54). *Table 1* demonstrates the results of group 1 with studies from large case-controlled series from high-volume centers focusing on their preferred technique. Regarding laparoscopic fundoplication the

**Table 1.** Overview on publications from large case-control series from high volume centers

Author; year Operative technique	n	Morbidity (Mortality) (%)	Follow-up Months (participation)	persisting dysphagia rate (%)	recurrent reflux (%)	good results (%)	Necessary Redo surgery (%)
Singhal 2018 (33) fundoplication	545	2.0 (mortality 0.2)	36 (73%)	4.0	12.0	88	4.3
Park 2018 (37) Hill repair	242	*	222 (38%)	16	30	76-85	16 dilation 9.9 redo surgery
Hakanson 2019 (38) fundoplication	456	227 Nissen: 4.4 229 Toupet: 4.8	36	*	Low * Nis = Tou	No difference	1.7 2.1
Hopkins 2020 (39) fundoplication	191	*	120	Nissen 6.9 Anterior 1.3	22 at 10y 39 at 10y	Nissen 84 Anterior 86	9.4 (Nissen 11.1; anterior 12.5)
Fuchs 2021 (40) fundoplication	1131	4 (mortality 0.09%)	67.2 (79%)	4.0	13.0	88.0	4.4 redo surgery
Buckley III. 2018 (41) MSA	200	2.5	8.6	1	8	94	9.5 dilations 1 redo surgery
Ayazi 2020 (42) Magnetic sphincter augmentation MSA	553	2.3	10.3	23.3	path DeMeester score: 17.6-34.3 %	86.7	17.9 dilations 6.7 redo surgery
Ferrari 2020 (43) MSA	335	*	108	4.8	21	89	2.4 dilations 9.2 revisional surgery
Hunter 2015 (44) Transoral Incisionless Gastropliation TIF	129	Adverse events: 11.6% over 108 months	6	1.1	11 at 6 months 32.3 at 18 months	68	*
Bell 2021 (45) Transoral Incisionless Gastropliation TIF	151	2.66	97 (86%)	*	30	64 (>50% QL- reduction)	22

• Rates not presented

selected studies concerned 2565 patients with GERD, operated by the laparoscopic fundoplication using different techniques of wrapping from partial anterior, partial posterior to complete Nissen-fundoplication.

The morbidity of the procedures ranged from 2.0-4.8% of cases. With a follow-up time of 36-222 months, most of these patients were followed > 5 years. The persisting dysphagia rate varied between 4 and 16% with an estimated median of 4.0%. Reflux recurrence occurred after this rather long follow-up time in 12.0-39%, with variations between the different wrap-techniques, indicating for the Nissen-version a recurrence rate of 12.0-22%, while for partial wraps 13.0-39%. Overall good results were documented in 76-88% with a necessity of revisional surgery in 1.7-12.5% of cases. The estimated median for the rate of redo-surgery was 4.4%.

The series of 1088 patients with Magnetic Sphincter Augmentation (MSA) showed (Table 1) a morbidity range of 2.3-11.6% and a follow-up period of 8.6-108 months. The

persisting dysphagia rate was shown to be 1-23.3% (estimated median: 4.8%) with a recurrent reflux rate of 8-34%. Good results were reported between 86-94%. Postoperative dilations were performed in 2.4-17.9% and revisional surgery, often device removal, was necessary in 1-9.2%.

A smaller series of 280 patients were documented in Table 1 after Transoral incisionless fundoplication (TIF). Adverse events range between 2.66-5.4%, while the follow-up period ranged between 6-97 months. The persistent dysphagia rate was reported only in one series with 1.1%. Reflux recurrence was quite frequent with 30-32% during the follow-up time. Overall good results were limited to 64-68% with a necessity for further endoscopic or surgical therapy in 22%.

The results of group 2, the analysis of comparative studies between several techniques of therapeutic antireflux procedures, multicenter-studies and meta-analyses of therapeutic GERD-trials, are shown in Table 2. In total, more than 150 studies and several

**Table 2.** Overview on publications from comparative studies, multicenter studies and meta-analyses

Author; year Operative technique	n	Morbidity (Mortality) (%)	Follow-up Months (participation)	persisting dysphagia rate (%)	recurrent reflux (%)	good results (%)	Necessary Redo surgery (%)
Kim 2021 (46) Funduplications Registry data	310	10.5	12	10.5	21.4	81	*
McKinley 2021 (47) Fundoplication vs PPI 102 studies	*	Surgical: 17.8	*	27.9	21-61	59-79	5.0 dilation 6.8 redo surgery
Skubleny 2017 (48) LINX vs Fundoplication 3 studies	688	(LINX: 415) 1.2 (Nissen: 273) 2.5	7-12 7-16	33.9 47.1	18.6 18.5	71.6 78.5	1.4 dilation
Asti 2018 (49) MSA in 13 centers	100	*	36	5	13	87	5 dilations 3.4 redo surgery
Aioffi 2018 (50) MSA vs fundoplication 7 studies	1211	MSA (n=686): 0-3 Fundopl. (n=525): 0-7 no mortality	6-12	9.3 6.6	17 13	83 87	2.3 2.0
Bonavina 2021 (51) MSA + funduplications	631	MSA: 465: 3.8 Fundoplication:166: 3.0	36	3.8 4.8	24.2 19.5	78.2 76.5	2.4 1.9
Jain 2016 (52) TIF 9 studies	443	3	6-36	0	28-82	52-77	3.1
Huang 2017 (53) TIF 18 studies	963	2.4 (Mortality 0.12%)	6	*	34	45-86	2.2 re-interventions
Testoni 2021 (54) TIF (TIF and MUSE) 8 studies	640	1.7	48	*	34-45	70.6	10 (0-37)

• Rates not presented

multicenter-registries were summarized in these 9 selected publications. The overall follow-up periods in these studies were substantially shorter with a range of 7-48 months with an estimated median of 16 months, compared to > 5 years in group 1.

Regarding multicenter-studies and meta-analyses around laparoscopic fundoplication we focused on 2 recent publications with more than 100 studies and a national registry with 310 patients. The morbidity concerning laparoscopic fundoplication was 10.5-17.8%, and thus clearly higher than the estimated median in group 1 (4%). Persisting dysphagia, a major draw-back of fundoplication, was reported in these studies within group 2 with a range of 10.5-27.9%. Furthermore, also the reflux recurrence was documented as high as 21.4-61% with an overall good result in 59-81%. Necessity of dilations and redo-surgery were in a similar range as in group 1.

A substantial number of studies in group 2 focused on the laparoscopic implantation of the MSA in 2630 patients. Morbidity was reported in 0-3.8% of cases. Persisting dysphagia was documented in a range of 3.8-33.9%, and recurrent reflux was documented in a range of 13-24.2%. Overall success rate for good results showed a range of 71.6-87%. Necessity for revisional surgery was limited between 1.4-3.4%.

The experience with TIF in trials on 2046 patients with GERD is also demonstrated in *Table 2*. Morbidity is at a rate of 1.7-3%, and it is noteworthy that there is mortality (0.12%) reported in one study for this endoscopic procedure. Post-therapeutic dysphagia seems to be low, since it was only rarely reported. Recurrent reflux seems to be a substantial problem with a range of 28-82%. The latter limits the overall success rate, which is reported to be between 45-86%. The re-intervention rate can be at 0-37%.

In summary, the results show a certain difference between study results from large case-controlled patient series from high-volume centers and results from multicenter studies and meta-analyses. Major differences between group 1 and group 2 exist for laparos-

copic fundoplication in reported morbidity and dysphagia rate. For MSA, these differences can be found in dysphagia and overall success rate. The results for TIF are quite similar in both groups.

## Discussion

For a correct comparison between different medical methods, a control group is necessary to make sure that the results are valid. Following evidence-based research, randomized controlled trials must be performed to establish results, which can lead to conclusions that can be transferred into clinical practice (55-60). Many randomized trials, and, furthermore, many meta-analyses of randomized trials have been performed to help in optimizing the interventional and surgical treatment for GERD (61-64). The drawback of these randomized trials is the necessary organizational and timely effort to perform these in a correct way. Ideally, to be tested all procedures should be performed under the same comparable conditions. This may be quite difficult, especially, if the surgical participants may have a different level of experience in one or the other procedure, involved in the comparative study. There are examples for this dilemma in literature.

Another problem is the increasing flood of meta-analyses. There are examples in literature in which a new method is introduced and published evidence is rather scarce, however, early attempts of meta-analyses already provide conclusions that may be misleading (65-68).

The weakness of this present analysis is the selection of publications for the demonstration of results, which may indicate a certain comparison, which is not acceptable under evidence-based rules. This study does not attempt to replace any conclusions about GERD-treatment from meta-analyses. However, the authors want to emphasize the value of well-studied and well-documented cohort results indicating the potential of high-end-specialization for one or the other endo-

scopic or surgical method in order to reach quality results beyond the usual study level. It is important to know what can be possible in contrast to results from multicenter or randomized studies (31,32,61,69). It must be also emphasized that such results are generated in a special condition or with special prerequisites and cannot be generalized.

For example, in the somewhat older literature one can find randomized trials in which the dysphagia rate, and subsequently the rate of revisional surgery after a Nissen fundoplication was as high as 15%, much higher than the rate after a Toupet posterior partial fundoplication (13,64,70). As a consequence, it is not surprising that in a subsequent meta-analysis, the results of a Nissen are much worse than a Toupet fundoplication (64). On the other hand, many large case-controlled studies show a revisional surgery rate for a fundoplication of < 5% (32,33,69). How should the critical reader interpret these two findings?

This manuscript is not focusing on the discussion between partial and total fundoplication, but focuses more on the potential level of good and excellent results, which can obviously be reached by both techniques, if the involved surgeons focus on one or the other technique of fundoplication (11,31-33,40,60, 61,69,71,72). In severe esophageal motility disorders, a partial fundoplication is advisable and can provide good results if selected and performed well (31,32,33).

Based on the level of the available evidence, the results of randomized trials have more value and are more valid, since these data are generated with a control group. But what if the surgeons involved did have much more experience with a Toupet techniques, compared to their experience with the Nissen technique, the comparison even in a randomized fashion is a problem.

The presentation of the different data from groups 1 and 2 in the tables should be considered as a confrontation of these partially controversial data, not a direct comparison. For the authors it is not only interesting, but also

important to provide data from a certain method, which can be reached with a high level of expertise and high volume of the team (33,37-43).

The results indicate that it seems to be important to focus with all possible components on a certain method and gain experience of many hundreds of cases, driving the idea of specialization further, to reach an optimized level of quality in the outcome of patients.

The results show that different modifications of fundoplication can be performed with a limited level of morbidity (around 4%), followed even in long follow-up by a limited level of persisting dysphagia and a success rate regarding Reflux-prevention above 85%. Magnetic sphincter augmentation can reach a similar success with lower initial morbidity, however, in most analyzed studies the severity of GERD was lower in the MSA-series compared to the fundoplication-series (41-43,48-51). This must be kept in mind when interpreting these data.

Neither in the large cohort-series nor in the meta-analyses TIF could reach similar results as the other two presented therapeutic techniques (33,37-54). This is not surprising since treatment of GERD necessarily combined with the anatomic correction of an associated hiatal hernia requires surgical anatomical dissection and changes, which is quite limited from inside the stomach.

## Conclusion

It can be concluded that special efforts in patient management in high volume centers and a vast experience may substantially contribute to excellent results for several antireflux techniques, which may reach a level of quality above results of registries, and meta-analyses. Surgeons and teams should be encouraged to strive for such a level of quality.

## Conflict of Interest

All authors declare that they have no conflicts of interests.

## Ethics of Approval

Ethical approval was not needed for this study.

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