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Long-term efficacy of transoral incisionless fundoplication with Esophyx (Tif 2.0) and factors affecting outcomes in GERD patients followed for up to 6 years: a prospective single-center study

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Abstract
Background Transoral incisionless fundoplication (TIF) with the EsophyX^{TM} device creates an antireflux valve with good functional results in patients with gastro-esophageal reflux disease (GERD). The aim of this study was to assess the long-term effect of TIF 2.0 on pathological reflux and symptoms in GERD patients with daily dependence on proton pump inhibitors (PPI).
Methods Fifty patients underwent TIF. All underwent GERD-HRQL and GERD-QUAL questionnaires, upper GI endoscopy, esophageal manometry, and 24-h pH-impedance before and 6, 12, and 24 months after TIF, and subsequent yearly clinical re-evaluation.
Results Patients were followed for up to six years (mean 52.7 ± 19.7 months). In all, 83.7, 79.6, 87.8, and 84.4 % of patients stopped or halved the PPI therapy 6, 12, 24, and 36 months after TIF. Three-year figure remained stable up to 6 years. Symptom scores off PPI were significantly lower at 6, 12, 24, and 36 months. At 6 months, Hill's grade I of the newly created valve persisted in all pre-procedure Hill's grade I patients, in 66.7 % of grade II and 58.3 % of grade III. This figure remained substantially unchanged at 12 and 24 months, too. Impedance monitoring indicated significantly fewer total and acid refluxes after treatment ($p = 0.01$). Factors predicting good outcomes were pre-procedure Hill's grade I-II, no hiatal hernia or hernia $\leq$2 cm ($p = 0.03$), absence of ineffective esophageal motility ($p < 0.0001$), and number of fasteners deployed ($p = 0.01$).
Conclusions TIF by the EsophyX achieved lasting elimination of daily dependence on PPI in 75–80 % of patients for up to 6 years. TIF seems an effective therapy for selected symptomatic GERD patients.

Keywords Gastro-esophageal reflux disease · Transoral incisionless fundoplication · Esophyx

In patients with gastro-esophageal reflux disease (GERD), antisecretory drugs and surgery relieve symptoms and improve the quality of life. However, both strategies raise some concerns. Medical therapy implies continuous long-term treatment, with potential drug intolerance or unresponsiveness. Furthermore, some patients need high dosages for long periods to prevent recurrences. Concerns related to surgery are the risk of creating new symptoms, such as dysphagia, flatulence, inability to belch, and bowel problems [1–3]. For these reasons, a variety of transoral endoscopic techniques aimed at reinforcing the barrier function of the lower esophageal sphincter (LES) have been proposed in the last 15 years as alternatives to antisecretory therapy or antireflux surgery, but have been abandoned because of disappointing long-term results.

Transoral incisionless fundoplication (TIF) using the EsophyX^{TM} device (EndoGastric Solutions, Redmond, WA, USA) is an endoscopic procedure that has been seen in the last few years to induce lasting improvement of GERD symptoms, cessation or reduction of proton pump inhibitor (PPI) therapy, and improvement of functional findings, measured by either pH or impedance monitoring.

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TIF by using Esophyx device has been proposed as an alternative treatment to surgery for those patients with typical gastro-esophageal reflux (GER) symptoms and small hiatal hernia, who are intolerant or unresponsive to PPI maintenance therapy.

TIF reconfigures the tissue to establish an omega-shaped, full-thickness gastro-esophageal valve from inside the stomach. The procedure was designed to create serosa-to-serosa plications which include the muscle layers and construct valves 3–5 cm long, taking in 200–300° of the circumference, deploying multiple non-absorbable polypropylene fasteners through the two layers (esophagus and stomach) in a circumferential pattern around the gastro-esophageal junction [4–6]. Previous studies reported the persistence of the newly created valve at 6 months and for up to 36 years, with good functional outcomes, judging from 24-h pH- and/or impedance monitoring [7–18]. However, like all new procedures introduced in clinical practice, despite favorable short-term outcomes, questions still arise about the long-term efficacy of the technique in controlling symptoms, and the duration of the newly created valve. In addition, we still need to clarify preoperative patient-related anatomo-functional findings and procedure-related technical aspects that can predict a successful outcome.

The aim of the present prospective, observational study was to evaluate the effect of TIF 2.0 technique on a) GERD-related symptoms, GER parameters, and endoscopic findings, assessed using GERD-HRQL and GERD-QUAL questionnaires, 24-h ambulatory pH-impedance, and upper gastrointestinal (GI) endoscopy repeated 6, 12, and 24 months after the TIF; b) GERD-related symptoms assessed by the GERD-QUAL questionnaires after 3 years and by telephone interview or outpatient consultation every subsequent year of follow-up, in a series of prospectively recruited consecutive patients.

Materials and methods

Over a six-year period (from January 2007 to December 2012), 50 patients underwent TIF 2.0 procedures for symptomatic GERD. The indication for TIF in all but two patients was symptomatic GERD, according to the Rome III criteria [19], pathological GER, and a positive correlation between symptoms and GER, documented by 24-h pH-impedance monitoring. Two patients had 24-h pH-impedance within the normal range but a positive correlation between symptoms and GER, and were responsive to high-dosage PPI. All patients complained of heartburn and/or regurgitation and had been on PPI maintenance therapy with a standard dose twice a day for at least 3 months before enrolment.

Fundoplication was done in all cases by a single endoscopist with in vivo experience in animal models and humans, after a curriculum-based training and first series of cases proctored by a surgeon with more than 200 cases experience at that time.

For each patient, clinical and procedural data were stored in a computerized database in the endoscopy unit.

Atypical symptoms of GERD, biopsy-proven Barrett's esophagus, esophageal stricture, hiatal hernia longer than 3 cm, previous esophageal, gastric or major abdominal surgery, and other severe co-morbidity (including cardio-pulmonary disease and collagen disease) were exclusion criteria for TIF.

All patients gave written informed consent for the procedure and for data management for scientific purposes, and the protocol was approved by the medical ethics committee of the San Raffaele Scientific Institute of Milan.

Study protocol

At enrolment, a full medical history was taken, including GERD medication, and all patients completed the GERD-HRQL and GERD-QUAL questionnaires while on a standard dose of PPI twice a day. PPI were then stopped for 14 days, and the patients were asked to complete the two questionnaires once again. Any drugs influencing gastrointestinal motility were also discontinued 14 days before the study.

They then underwent

- Upper GI endoscopy to determine the Hill's grade and Jobe length of the gastro-esophageal valve; the presence and size of hiatal hernia; the presence and severity of esophagitis according to the Los Angeles grading system [20];
- Stationary esophageal manometry and 24-h ambulatory pH-impedance monitoring;
- Scintigraphic recording of gastric emptying time.

Post-operative outpatient assessment at weeks 1 and 2 was scheduled by telephone.

GERD-HRQL and GERD-QUAL questionnaires, PPI consumption, upper GI endoscopy, esophageal manometry, and 24-h ambulatory pH-impedance were repeated 6, 12, and 24 months after the TIF. Ambulatory pH-impedance was done when off PPI, in patients who had been still taking them.

GERD-HRQL and GERD-QUAL questionnaires and PPI consumption data sheets were also completed again after 3 years. In the subsequent years of follow-up, information about GER-related symptoms and PPI consumption was obtained every year by telephone interview or office consultation. The scores at follow-up were obtained off PPI even in patients who were taking PPIs, after a therapy's discontinuation of 14 days. PPI consumption was considered "continued" when the daily drug dose was the same

as before the procedure; "reduced" when any daily dose was taken for less than half the total number of days during follow-up; and "completely stopped" when not one dose of PPI was taken during the follow-up.

GERD-HRQL and GERD-QUAL questionnaires

The GERD-HRLQ is a validated 10-item questionnaire that measures the symptom severity of GERD patients [21]. Six items measure satisfaction for the degree of heartburn, two for dysphagia/pain while swallowing, one for the impact of medication on daily life; one item measures overall satisfaction with the present condition. Regurgitation scores were assessed with six questions similar to those used to assess heartburn score and included in the GERD-HRLQ score calculation. Each item is scored from 0 to 5.

The GERD-QUAL is a validated 37-item questionnaire that measures the quality of life of GERD patients [22]; each item is scored from 1 to 5.

Geometry of the gastro-esophageal valve

The geometry of the gastro-esophageal valve was investigated by measuring the Jobe length, defined as the distance (in centimeters) from the apex of the fundus to the valve lip using standard biopsy forceps with open valves (7 mm wide), and the Hill's grade, as described in previous studies [9, 14, 23–25].

Stationary esophageal manometry

Patients fasted overnight, and then a 12-Fr diameter, water-perfused PVC catheter for esophageal manometry with six recording side holes (Bioengineering Laboratories SpA, Como, Italy) was introduced trans-nasally. Esophageal manometry was then done in the standard way with a stationary pull-through technique for localization and measurement of the resting pressure of the LES and esophageal motor function [26]. Tracings were classified according to Spechler et al. [27].

24-h pH-impedance monitoring

The 6-Fr MII-pH disposable catheter consists of eight impedance rings at −3, −1, 1, 3, 5, 9, 11, and 13 cm from markings, and a pH electrode at 0 cm (VersaFlex^{TM} Z, Alpine Biomed Corporation, USA). After calibration, the probe was placed 5 cm above the upper margin of LES manometrically identified.

Patients were given personal diaries to note meal times, medication intake, time in the recumbent position, and the timing of GER-related typical symptoms. Data were recorded on a portable recorder (Ohmega, Ambulatory pH & impedance recorder, Medical Measurement System, MMS, Netherlands) and analyzed using the MMS analysis program (MMS, Netherlands); the accuracy of reflux detection was verified manually by an experienced reader. Tracings were classified according to Zerbib et al. [28]. Symptom correlation was considered significant when the symptom association probability (SAP) was ≥95 % [24]. Johnson–DeMeester scores higher than 17 were considered abnormal [29].

Gastric emptying time by scintigraphy

Gastric emptying time was measured by scintigraphy after patients had eaten a standardized Tc-99 meal. The half-emptying time (t ½) was recorded; a mean emptying time of 62 ± 11 min was considered normal [30].

Transoral incisionless fundoplication (TIF 2.0) with the EsophyX^{TM} device

The EsophyX^{TM} device was inserted trans-orally over a standard front-view endoscope (Pentax EG 2770 K) with the patient under deep sedation with Propofol (Diprivan®, AstraZeneca, Italy) in the left lateral position. The device enables tissue manipulation and plication, and polypropylene suture material is placed in the region of the gastro-esophageal junction. One endoscopist operated the device and controlled the tissue manipulation and wrap around the distal esophagus as well as the implantation of fasteners, while another operated the endoscope and ensured continuous visualization and insufflation during the procedure, as reported previously [4, 5]. Deployment of fasteners was started in all patients on the far posterior and anterior sides of the gastro-esophageal valve along the lesser curvature. In the last 22 patients, at the posterior and anterior sides of the gastro-esophageal valve, the tissue mold was rotated axially to wrap the stomach over the esophagus, tightening the circumference and resulting in a valve circumference of >240°; two sets of fasteners were deployed at each site [6]. A satisfactory partial fundoplication was confirmed intra-operatively on the basis of an endoscopic finding of a well-defined nipple valve. At the end of the procedure, Hill's grade and Jobe length of the newly created valve and the number of fasteners deployed were recorded. Post-procedural management was described in our previous papers [9, 13].

Statistical analysis

Intra- and inter-patient characteristics, GERD-HRLQ and GERD-QUAL total scores, and morphological and functional findings were compared by Wilcoxon's and Mann–Whitney tests or Fisher's exact test, as appropriate. Binary

logistic regression was used to test predictors of outcomes. A p value <0.05 was considered statistically significant. Data are presented as mean ± SD.

Results

Thirty-five patients were men (70.0 %), the overall mean age was 45 ± 16 years, and the mean body mass index (BMI) was 22 ± 3 kg/m2. Mean GERD-related quality of life scores (GERD-HRQL and GERD-QUAL) were, respectively, 20 ± 13 and 84 ± 20 on PPI and 46 ± 19 and 114 ± 20 off PPI therapy (having discontinued PPI for at least 14 days before enrolment); the differences were significant ($p < 0.01$). Thirty-six patients (72.0 %) were completely responsive to a standard dose of PPI twice a day, twelve (24.0 %) were partially responsive (defined as a GERD-HRQL score >12 on standard doses twice a day for at least 4 weeks), and two were not responsive at all (4 %).

Endoscopic examination indicated that 28 of the 50 patients (56.0 %) had hiatal hernia: 1–2 cm long in 26, 2.5 cm in one, and 3 cm in another. Ten had grade A esophagitis and one grade B. The Hill's grade of the gastro-esophageal valve was I in three patients, II in 34, III in 12, and IV in one. The mean Jobe valve length was 0.98 ± 0.5 cm. Stationary manometry showed ineffective esophageal motility (IEM) in 18/50 patients (36.0 %). Mean gastric emptying time was abnormally long (80 ± 38 min) in 24 patients (48.0 %).

TIF 2.0 procedure

Fifty-one TIF 2.0 procedures were done in the 50 patients. In all, TIF 2.0 was successful in 49 patients, with a mean duration of 69 ± 19 min. Two procedures were interrupted, one after the deployment of only a few initial fasteners, as a pneumothorax occured; the second one, for device malfunction, was repeated with success. A mean of 12 ± 4 fasteners was deployed to construct each valve. Hiatal hernias, if present, were always reduced. In all cases, the Hill's grade of the newly created valve was I, and its mean length was significantly greater than before the procedure (2.7 ± 0.4 vs. 0.98 ± 0.5 cm; $p < 0.01$).

Severe complications arose in two of the 51 procedures (3.9 %), both pneumothoraxes. In both cases, the complication was confirmed by X-ray immediately after the procedure, and managed by immediate trans-thoracic drainage. Both patients had rapid resolution of the pneumothorax and were discharged from hospital within 3 days.

All patients complained of mild to moderate epigastric pain in the four to 6 h after the procedure, requiring analgesics in 22 cases (44.0 %); 32 patients (64.0 %) complained of 24-h pharyngeal irritation, as a result of insertion and manipulation of the device. Six patients (12.0 %) reported mild epigastric pain persisting for 3–5 days, but not requiring analgesics. None of the patients reported either dysphagia or gas bloating.

Follow-up

The overall mean follow-up was 52.7 ± 19.7 months (range 20.3–75.0). All 49 patients in whom TIF 2.0 was successful received a complete follow-up examination at 6 and 12 months, 45 at 24 months, and 32 at 36 months. Twenty-four patients were clinically re-evaluated at 4 years, 19 after 5 years, and 14 after 6 years. Three patients were followed for 7 years and longer but, because the number was so small, we considered the six-year results for the present study.

Four patients unresponsive at 12 months underwent surgical Nissen fundoplication; all had preoperative Hill's grade of the valve III or more. Only one of them stopped PPI therapy after surgery. One patient was lost at the six-year follow-up (not contactable).

GER-related symptoms

The GERD-HRLQ and GERD-QUAL scores off PPI therapy were significantly lower than before treatment at 6 and 12 months, and 2 and 3 years (Table 1).

Symptomatic responses were assessed 6 months and 1–6 years after TIF and classified according to proton pump inhibitor (PPI) use as follows: complete responders were patients who completely stopped using PPI; partial responders patients who halved the previous PPI dose; non-responders patients who still used the pre-TIF PPI dose (Fig. 1).

Six months after the procedure 30/49, 11 and 8 patients had stopped daily PPI altogether, had reduced it by more than half, and were taking the same dose as before the procedure, respectively. In all, 41 patients (83.7 %) stopped or halved the PPI therapy 6 months after TIF.

Twelve months after TIF, respectively, 25/49, 14, and 10 patients did not need PPI, had reduced their anti-secretive medications, or were still on daily PPI, respectively. More than three quarters of the patients (79.6 %) stopped or halved PPI therapy 12 months after TIF.

Forty-five patients were evaluated 24 months after TIF. In nine cases (20.0 %), TIF was unsuccessful: five were still using the same PPI dose as before the procedure, and four underwent Nissen fundoplication and were no longer evaluated. Twenty-three did still not need any PPI, and 13 were using less than half the previous dose. Overall, 36/41 (87.8 %) patients still in follow-up at 24 months were not taking PPIs or had halved the dose.

Table 1 Mean GERD-HRLQ and GERD-QUAL scores on and off therapy before TIF, and off therapy 24 and 36 months after TIF

	Pre-TIF ON	OFF	p*	24 months after TIF OFF	p**	36 months after TIF OFF	p**
GERD-HRLQ	20 ± 13	46 ± 19	<0.01	16 ± 13	<0.01	17 ± 14	<0.01
GERD- QUAL	84 ± 20	114 ± 20	<0.01	71 ± 24	<0.01	80 ± 21	<0.01

* p ON vs. OFF therapy; ** p OFF after vs. OFF before TIF

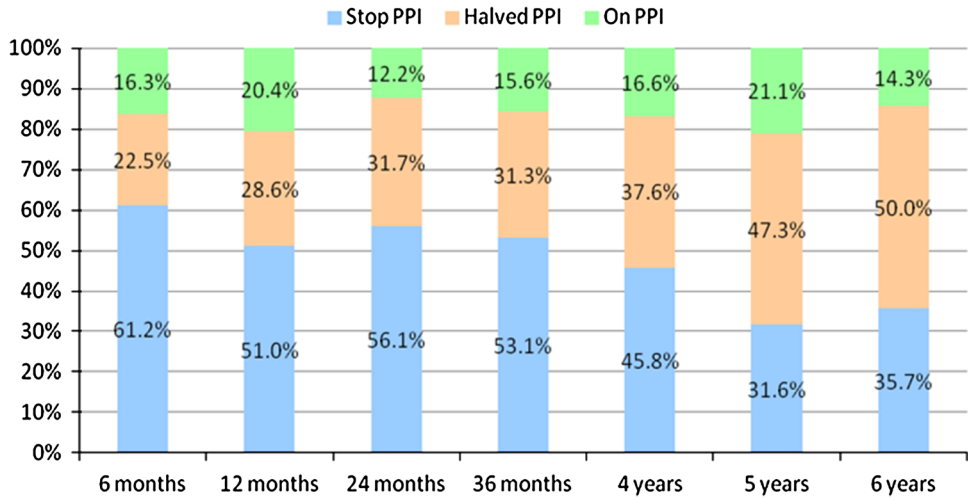

Fig. 1 Symptomatic responses 6 months and 1–6 years after TIF. "Complete or partial responders" patients versus "non-responders" patients: 12 months versus 6 months after TIF $p = 0.8$; 24 months versus 12 months $p = 0.4$; 36 months versus 24 months $p = 0.7$; 4 years versus 36 months $p = 1.0$; 5 years versus 4 years $p = 1.0$; 6 years versus 5 years $p = 1.0$

After 3 years, 17 of the 32 patients still in follow-up, 10 and 5 had completely stopped PPI, had halved PPI therapy, and were still on daily anti-secretive therapy, respectively. Thus, 27 (84.4 %) of these patients had either stopped or halved their PPI therapy, and five were using the same dose as before or underwent surgery.

Four, five, and six years after TIF, respectively, 20/24 (83.3 %), 15/19 (78.9 %), and 12/14 (85.7 %) patients had stopped or halved the PPI therapy; the percentages remained substantially stable and similar to that at 3 years.

Percentages referring to symptomatic response 6 months and 1–6 years after TIF are reported in Fig. 1.

Dividing the patients on the basis of PPI use and considering as responders to TIF, only those who completely stopped this therapy, 61.2, 51.0, 56.1, 53.1, 45.8, 31.6, and 35.7 %, respectively, were full responders at 6, 12, 24, and 36 months and 4, 5, and 6 years. The complete response rate 3 years after the intervention was 8 % lower than at 6 months, but the difference was not significant ($p = 0.5$). At the 5-/6-year follow-up, the complete response was maintained in approximately 30 % of patients, and was half the six-month results. In fact, 5–6 years after TIF, approximately half the patients with a complete response at 3 years had gone back to taking PPIs, but at half the doses, they had been using before.

Considering as non-responders only those who were still on daily PPI therapy, respectively, 16.3, 20.4, 12.2, 15.6, 16.6, 21.1, and 14.3 % of patients had no benefit from TIF at 6, 12, 24, and 36 months and 4, 5, and 6 years; the rates did not change significantly over time.

Intention-to-treat analysis of the effect of TIF on PPI use, including all the 50 patients scheduled to undergo the procedure, showed that at 12 and 36 months, 39/50 (78.0 %) and 27/33 (81.8 %) patients had stopped or halved PPI therapy ($p = 0.8$); 25/50 (50.0 %) and 17/33 (51.5 %) had completely discontinued it.

Functional findings

LES pressure and DEA did not change significantly after treatment at 6, 12 and 24 months; however, impedance monitoring showed there were significantly fewer total and acid refluxes after treatment ($p = 0.01$). The percentage of refluxes reaching the proximal extent tended to be lower whereas the number of weakly alkaline refluxes was not significantly different. The weakly acidic refluxes decreased after treatment, though not significantly. The Johnson–DeMeester score did not change. Table 2 compares these results with the pre-TIF findings.

Morphological findings

At the six-month endoscopic follow-up, 17/28 patients (60.7 %) no longer had hiatal hernia; however, it recurred in the two cases with pre-procedure hernias >2 cm and in 9/26 patients (34.6 %) with hernias ≤2 cm. At 12 and

24 months, hiatal hernia recurred in three more cases. Overall, at 24 months, 14 cases still had hiatal hernia (50.0 %) (Fig. 2).

The newly created valve was still Hill's grade I six months after TIF in 32/49 patients (65.3 %): in all pre-procedure Hill's grade I cases, in 22/33 with grade II (66.7 %), and 7/12 (58.3 %) with grade III. The patient with Hill's grade IV returned to the pre-procedure grade. The six-month Hill's grade of the newly created valve remained substantially unchanged at 24 months (Fig. 3).

The mean Jobe length of the newly created valve at 6 months stayed at the immediate post-procedure value and remained substantially unchanged at 12 and 24 months, independently from the pre-procedure Hill's grade (2.68 ± 0.4 for Hill's grade I and 2.70 ± 0.4 for the higher grades).

Grade A esophagitis was present at 6, 12, and 24 months in 3/11 patients (27.3 %): 2/10 (20.0 %) had pre-procedure grade A and one grade B, and it appeared in 3.

Pre-procedure and procedure-related findings affecting TIF 2.0 outcomes

Twelve of the 30 full responders (40.0 %) at 6 months had hiatal hernia, always ≤2 cm, and 14 of the 19 non- or partial responders (73.7 %) ($p = 0.03$). The two patients with hiatal hernia >2 cm were non-responders. Hiatal hernia <2 cm was associated with 80.0 % of full responses (8/10 patients), and hernia ≥2 cm with 22.2 % (4/18 patients) ($p = 0.013$).

Twenty-five of the 30 full responders (83.3 %) had Hill's grades I and II before TIF; among the 19 non- or

Table 2 Esophageal motility and pH-impedance findings in GERD patients before, 6 and 24 months after TIF

	Pre-TIF	6 months after TIF	p*	24 months after TIF	p**
Esophageal manometry					
LES pressure (mm Hg)	8 ± 3	11 ± 3	0.12	12 ± 2	0.7
DEA (mm Hg)	72 ± 31	77 ± 27	0.77	75 ± 31	0.8
pH-metry					
Johnson–DeMeester score	22 ± 12	18 ± 15	0.47	19 ± 20	0.4
Impedance					
Total refluxes (no.)	66 ± 40	38 ± 37	0.01	43 ± 35	0.5
- Acidic	40 ± 23	12 ± 10	0.001	14 ± 11	0.5
- Weakly acidic	22 ± 20	13 ± 8	0.22	12 ± 10	0.4
- Weakly alkaline	2 ± 9	3 ± 12	0.71	5 ± 12	0.4
- Proximal	28 ± 19	15 ± 12	0.1	14 ± 9	0.5
- % proximal	41 ± 19	28 ± 19	0.06	30 ± 19	0.7

LES lower esophageal sphincter, *DEA* distal esophageal amplitude

* p 6 months after TIF vs. pre-TIF; ** p 24 months after TIF vs. 6 months after TIF

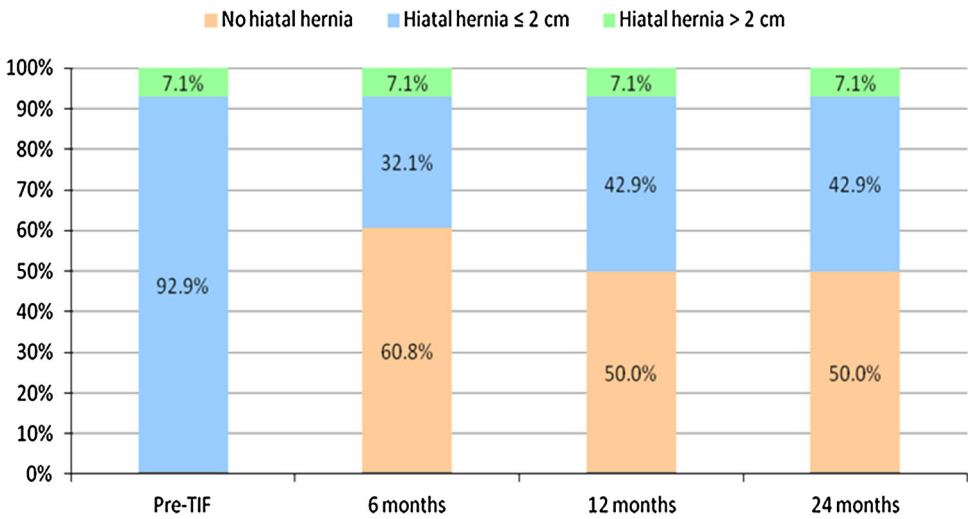

Fig. 2 Hiatal hernia (HH) in patients before and 6, 12, and 24 months after TIF

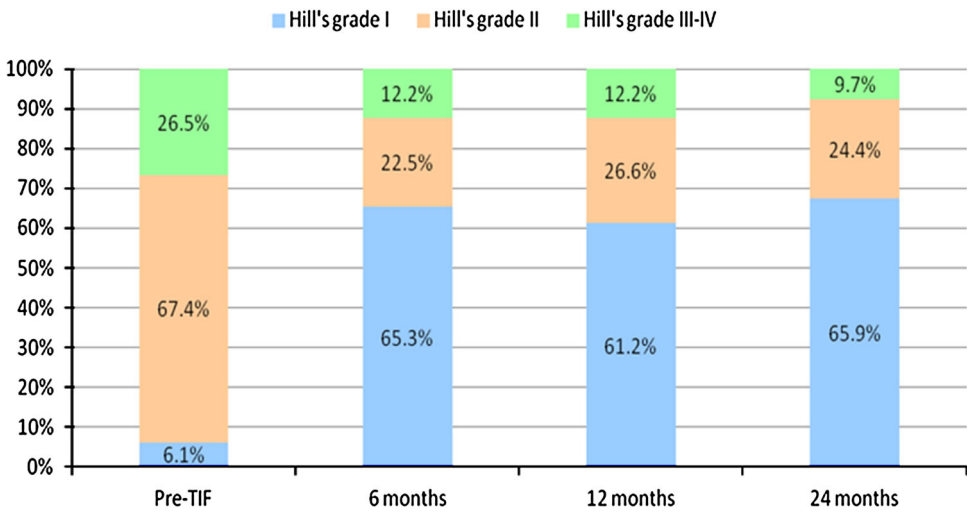

Fig. 3 Hill's grade in patients before and 6, 12, and 24 months after TIF

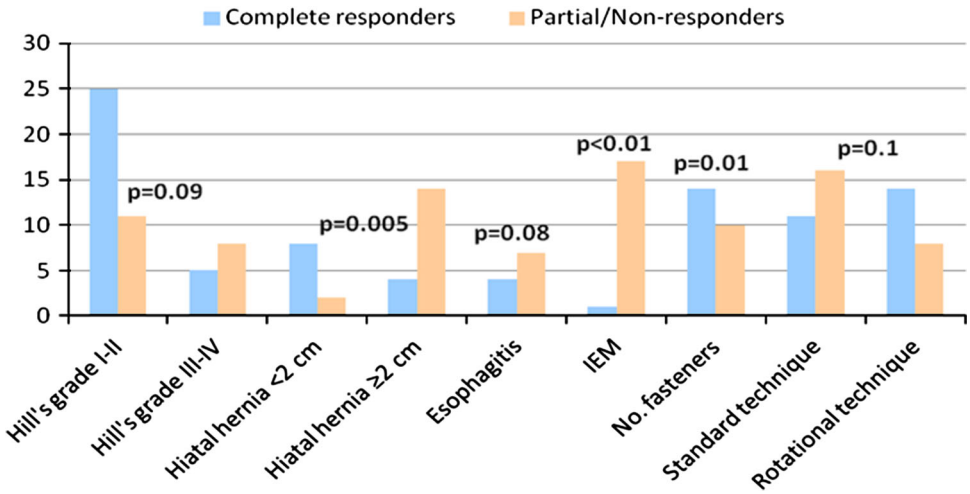

Fig. 4 Pre-TIF and TIF-related findings in "complete responders" (30 patients) and in "partial/non-responders" (19 patients), defined as complete cessation of PPI therapy and partial or no cessation of PPI therapy, at 6–12 months in 49 patients *IEM* ineffective esophageal motility

partial responders, 11 (57.9 %) had grades I and II ($p = 0.09$). Hill's grades I and II were associated with 69.4 % of full responses (25/36 patients) and grades III and IV with 38.5 % (5/13 patients) ($p = 0.09$). At 24 months, 16/22 full responders (72.7 %) had had a Hill's grade I valve at 6 months; among the nine non-responders, including those who underwent surgical fundoplication, seven (77.8 %) had a valve more than grade II.

Pre-procedure esophagitis was reported in 4/30 responders (13.3 %) and 7/19 non- or partial responders (36.8 % $p = 0.08$). Esophagitis persisted or recurred after TIF only in non-responders. Esophageal motility was abnormal in 17 of the 19 non- or partial responders (89.5 %) and 1/30 responders (3.3 %) ($p < 0.0001$).

With the standard TIF2.0 technique, 11/27 patients (40.7 %) were full responders at 12 months; with the application of the rotational TIF 2.0 technique, 14/22 patients (63.6 %) were full responders ($p = 0.15$). Responders had more fasteners released during the TIF than non-responders (10 ± 2 vs. 14 ± 2; $p = 0.01$). Data are summarized in Fig. 4.

Patient-related factors identified as significant in the prediction of a 12-month successful outcome were no pre-procedural hiatal hernia or hiatal hernia ≤ 2 cm and no abnormality in esophageal motility. A good predictor of successful outcome—though not significant—was Hill's grades I and II of the valve. Technique-related factors were the number of fasteners released, which was a significant predictor of outcome ($p = 0.01$); a larger number of fasteners raised the probability of being a responder about fourfold. Gastric emptying time, esophagitis, and the characteristics of GER, indicated by 24-h pH-impedance monitoring, were not significant predictors of outcome. The TIF 2.0 rotational technique, although it gave a 50 % increase in good results, was not significant either.

Discussion

The present study assessed the efficacy of the TIF 2.0 procedure and TIF 2.0 rotational procedure on GER-related symptoms for up to 6 years and morphological and functional findings up to 2 years, in a series of consecutive patients with documented GERD, treated by a single endoscopist in a single center. The study also attempted to identify anatomical, functional, and procedure-related factors influencing a successful outcome. To our knowledge, this is the first study of post-TIF results in GERD patients, assessed on the basis of daily PPI dependence, for up to 6 years. Although the number of patients followed up at 5 and 6 years is relatively small, outcomes were similar to those at 3 years and very likely reproducible for all cases undergone TIF in our series.

The study was carried out in a carefully selected group of patients with chronic GERD who were not satisfied with medical therapy.

Symptomatic assessment with the GERD-HRLQ and GERD-QUAL questionnaires gave significantly lower scores off PPI therapy than before treatment. Three-year results appeared to remain stable up to 6 years, at clinical evaluation.

Six months after TIF, the clinical results substantially confirmed those we reported in a previous smaller series: 83.7 % of patients stopped or halved PPI therapy. Twelve, 24, and 36 months after TIF, daily high-dosage PPI dependence was eliminated in, respectively, 79.6, 87.8, and 84.4 % of patients, and that proportion was maintained up to 6 years, providing further evidence of the lasting effect of TIF on symptoms and PPI usage.

Considering as responders only patients who completely stopped PPI therapy, the results were less satisfactory, with rates varying from 61.2 to 53.1 % during the first 36 months after the procedure, and falling to about 30 % at 5 and 6 years. In the 3 years after TIF, there was an 8 % drop in complete responses from the six-month situation. The difference was largest (10 %) between six and 12 months, while between 12 and 36 months, the results did not substantially differ. The changes confirm that factors negatively affecting post-operative outcomes play a role early in the post-operative period. These findings also support the notion that appropriate patient selection plays a pivotal part in achieving complete clinical success after TIF.

Although the lack of a control group in our study cannot rule out a placebo effect in the short post-TIF period, symptom control persisting for three to 6 years very likely indicates there was no such effect in the first 6–12 months. Figures up to 3 years on symptom outcomes are similar to those recently reported in the only three-year follow-up study on TIF so far published [17].

Morphological assessment indicated that the Hill's grade of the newly created valve remained I in 61.2 % of cases at 12 and 65.8 % at 24 months after TIF. At 24 months, grade I persisted in 63.6 and 33.3 % of patients with preoperative grade II and III, respectively, in 40 % with hiatal hernia smaller than 2 cm, and in none with preoperative Hill's grade IV or hiatal hernia larger than 2 cm.

In our hands, the TIF technique was unable to retract enough tissue from the fundus to create a robust and persistent valve. In this clinical setting, patients with Hill's grade I and II valves and hiatal hernia $\leq$2 cm were the best candidates for successful TIF.

The mean Jobe length remained the same as immediately after the procedure in all patients with persisting Hill's grade I, but was shorter in the others. The six-month Hill's grade and mean Jobe length of the new valve remained substantially unchanged at 12 and 24 months, again confirming that unsuccessful outcomes depending on patient- and technical-related factors occur within 6–12 months after the procedure.

The manometric and pH-impedance findings confirm our previous data [13], but in a larger series: the numbers of total and acid refluxes, measured by impedance monitoring, were significantly lower, while the LES basal pressure, DEA, and Johnson–DeMeester score did not change significantly. Discordance between the relief of overall symptoms and conflicting motility test findings has also been reported in studies of the outcomes of TIF and other endoscopic procedures for GER [13, 31]. This suggests that with the present technique, it is probably more the greater length of the newly created valve (more accurately measurable by endoscopy rather than by standard manometry) than its pressure that acts as a barrier to reflux; this mechanism may also explain the sustained response over time, despite the worsening of the Hill's grade of the valve in some patients.

Overall, in our series, three- to six-year post-TIF results were inferior to those reported in patients operated by surgical total 360° fundoplication (Nissen), but similar to those with surgical posterior partial (Toupet) or anterior partial (Dorr) fundoplication [32, 33], without any of the surgery-related side effects such as dysphagia and gas bloat. The other series of TIF so far published have also reported no long-term side effects or procedure-related symptoms. Re-intervention after laparoscopic fundoplication was reported in up to 14 % of cases [1], and TIF has been successful after failed surgical fundoplication, too [34]. On the other hand, surgical fundoplication is feasible after failed TIF, with no particular technical difficulties or increased morbidity [35, 36]. In our series, 8.1 % of cases underwent a surgical revision for TIF failure but in all these patients, the TIF was done early in the operator's learning

curve with an experienced surgeon present as proctor when needed in initial cases. A retrospective study in 124 unselected patients older than 60 years carried out in two community hospitals and based only on clinical assessment confirmed that the operator's experience plays a major role in successful outcomes; it reported, respectively, 75 and 80 % of patients free of typical and atypical GER symptoms in a mean follow-up of 7 months [37].

In other series, surgical revision after TIF failure was reported in from 10.6 to 18.0 % of cases [17, 35, 36]. Worse outcomes after TIF were reported in two studies, which found, respectively, 66.7 and 68 % of non-responders after 12 months in a small series of patients and with a short follow-up [38, 39]. An open-label study comparing TIF with robot-assisted Nissen fundoplication in PPI-refractory GERD patients reported complete symptom remission and normalization of esophageal acid exposure time in 30 and 100 % of patients after TIF and 50 and 100 % after Nissen fundoplication. This suggests that in a challenging clinical setting such as PPI refractoriness, Nissen fundoplication is at present more effective than TIF [40].

It cannot be excluded that the current lower efficacy of TIF compared with surgical Nissen fundoplication may be related to the particular subset of patients who underwent TIF, who had less impairment of the gastro-esophageal junction, and in whom GERD-related symptoms might be generated by a number of complex mechanisms besides the reflux, including increased esophageal sensitivity to refluxate. In fact, three out of four patients in our series who underwent Nissen fundoplication still did not improve. Further data are needed to clarify this point.

TIF was associated with a major complication in two of our cases (3.8 %). In both, pneumothorax occurred as a result of pleural perforation caused by insertion of the needle close to the lesser gastric curve and possibly capture of the diaphragm. This sort of complication should therefore be borne in mind when attempting to create a very tight valve. The overall complication rate reported so far ranges from 3 to 10 %, and includes bleeding, mucosal tears or perforation, pneumothorax, and mediastinal abscesses.

Looking at factors affecting the outcomes of TIF 2.0 in our series, six-month persistence of a Hill's grade I valve allowed patients to stop using PPIs completely, even for a long period; preoperative Hill's grades III and IV and hiatal hernia larger than 2 cm both negatively affected the persistence of Hill's grade I of the valve, and therefore TIF outcomes. The number of fasteners deployed and the rotational technique applied were associated with a good outcome, too; a larger number of fasteners raised the probability of being a responder about fourfold. The loss of effectiveness of TIF 2.0 early in our experience might be partially explained by the relatively small number of fasteners deployed when we started using the technique. The number of satisfactory fasteners is unquestionably a critical point for the success of the procedure, as stated in another paper [6]. The rotational technique raised the probability of being a responder by one half, confirming other recent reports [6, 18].

Among functional findings, ineffective esophageal motility was the sole condition predicting a higher rate of unsuccessful results, in terms of GER-related symptoms, possibly because the defective clearance of refluxate induces epithelial sensitization that might induce symptoms, even in cases with only low-volume GER [41]. Ineffective esophageal motility is a problem seen in a heterogeneous group of subjects with different manometric subsets and different symptom profiles, who might respond to a procedure in different ways [42]. Further studies on larger series of patients are needed to confirm the role of ineffective esophageal motility as an independent predictor of TIF's failure. On the other hand, TIF could be a valuable treatment option for patients who are at high risk of developing persistent post-surgical dysphagia because of ineffective esophageal motility.

We did not consider among the preoperative factors affecting TIF outcomes symptom and reflux scores, as reported in a recent univariate and multivariate analysis study [43].

Our results are similar to most of the 11 follow-up studies so far published: eight reported good symptomatic and objective outcomes, in from 75 to 82 % 6 months after TIF [7–10, 12–14, 17, 18], 76–85 % at 12 months [7–9, 14, 15, 17], and 75–93 % at 24 months [8, 14, 17]. Only two studies, including the present one, reported three-year outcomes regarding discontinuation of daily PPI, with rates of 74 % [17] and 75.8 % in our series.

In conclusion, in this follow-up study, we found that TIF 2.0 by Esophyx achieved long-lasting elimination of daily dependence on PPI in 75–80 % of cases for up to 6 years, and about 50 and 30 % of patients could stop PPI medication in, respectively, 3 and 6 years, with no troublesome persisting procedure-related side effects. The procedure also significantly reduced the GER episodes up to 2 years, as measured by pH-impedance recording.

Three- to six-year follow-up outcomes were substantially similar to those reported for partial anterior or posterior surgical fundoplication, but worse than for total 360° fundoplication. Most of the prospective TIF follow-up studies showed similar results up to 3 years. The number of fasteners deployed significantly affected post-operative outcomes, and the rotational technique appeared markedly, but not significantly, to increase the successful outcomes.

Although no randomized controlled trials are available yet, TIF fundoplication may offer an effective and safe

therapeutic option for carefully selected symptomatic GERD patients, with Hill's grade of the valve I and II or hiatal hernia $\leq$2 cm, who refuse life-long medical therapy or surgery, are intolerant to PPI, or have some risk of developing persistent post-surgical side effects.

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