



Original article

Sleeve gastrectomy and gastroesophageal reflux: a comprehensive endoscopic and pH-manometric prospective study

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Abstract

Background: The impact of sleeve gastrectomy (SG) on gastroesophageal reflux disease (GERD) is still greatly debated. Most of the current evidence available is solely based on symptom evaluation or medication use, while a minority have implemented objective functional measurements.

Objective: To better comprehend the pathophysiological mechanisms involved in the genesis of GERD after SG.

Setting: University Hospital, Italy.

Methods: A total of 21 patients affected by morbid obesity and eligible for SG were prospectively enrolled in the present study. Patients were evaluated by means of endoscopy, high-resolution manometry (HRM), 24-hour pH monitoring, and the Gastroesophageal Reflux Disease Health-Related Quality of Life questionnaire.

Results: Follow-up was completed at least 1 year post operation (mean follow-up, 14.3 ± 2.1 mo) by 19 patients. Body mass index decreased from 41.2 ± .9 to 26.8 ± .8 kg/m² ($P < .001$). Distal contractile integral significantly decreased from 2772.8 ± 399.9 mm Hg/s/cm to 2060.4 ± 338.9 mm Hg/s/cm ($P = .01$). The 24-hour pH monitoring showed an overall reduction tendency of acid reflux, although this was not statistically significant. All analyzed endoscopic findings withstood substantial pejorative modifications after SG ($P < .01$). Distal contractile integral values at baseline predicted postoperative Z-line upward migration; HRM, distal latency, and DeMeester score at baseline predicted the development of erosive esophagitis at follow-up, by bootstrap estimates of a logistic regression.

Conclusions: Postoperative GERD-related esophageal sequelae should be carefully considered after SG. Our results demonstrate how acid reflux does not seem to play a relevant role in the pathophysiology of post-SG GERD. Baseline HRM can help stratify the risk of developing erosive esophagitis and Z-line upward migration after SG, while postoperative endoscopic surveillance should be encouraged regardless of the presence or absence of symptoms. (Surg Obes Relat Dis 2020; ■:1–9.) © 2020 American Society for Bariatric Surgery. Published by Elsevier Inc. All rights reserved.

Keywords:

Sleeve gastrectomy; Gastroesophageal reflux disease; Endoscopy; High-resolution manometry; 24-hour pH monitoring

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Morbid obesity has turned into a global epidemic resulting in a soaring economic burden [1]. Bariatric surgery is at present the most efficacious long-term treatment for the cure of obesity and co-morbid conditions and its use is rising in parallel to this pandemic. Among bariatric procedures, sleeve gastrectomy (SG) is the most frequently performed, representing 45.9% of all operations worldwide [2].

Gastroesophageal reflux disease (GERD) and hiatal hernia (HH) are closely associated with obesity and have been positively correlated to the development of Barrett's esophagus (BE) [3]. Furthermore, augmented central adiposity or excess body mass index (BMI) per se have also been clearly linked to BE, regardless of the coexistence of GERD [4].

The postbariatric resolution of obesity has not been univocally associated to an improvement of GERD symptoms. It is indeed the type of bariatric operation selected that is implicated in this mechanism. In fact, Roux en Y gastric bypass (RYGB) has been shown to be the most successful in inducing GERD improvement or remission [5]. On the contrary, the impact of SG on GERD is still under debate. Some authors have shown an aggravation or increased incidence of de novo GERD after SG, while others have demonstrated its reduction. Nevertheless, most of the current evidence available is based on symptom evaluation or medication use, while a limited number of studies have actually implemented objective functional measurements [6,7].

The onset or worsening of GERD after SG is multifactorial and has been attributed to the absence of the gastric fundus with abolition of the angle of His, increased intraluminal pressure, division of sling fibers and/or phrenoesophageal ligament causing decreased lower esophageal sphincter (LES) pressure, antral pump loss due to a radical resection of the antrum, middle gastric stricture with delayed gastric emptying, and HH with intrathoracic migration of the gastric sleeve [7].

To better comprehend the pathophysiological mechanisms involved in the genesis of GERD, EE, and finally BE after SG, we prospectively evaluated patients by means of endoscopy, high-resolution manometry (HRM), 24-hour pH monitoring, additionally correlating the emerging objective findings to the reported GERD symptoms through the Gastroesophageal Reflux Disease Health-Related Quality of Life (GERD-HRQL) questionnaire.

Methods

Study design

Between October 2017 and August 2018, a total of 21 patients affected by morbid obesity with a mean BMI of $41.2 \pm .9 \text{ kg/m}^2$ and eligible for SG were prospectively enrolled in the present study. All patients underwent the standard preoperative multidisciplinary workup following institutional, national, and international guidelines, involving complete

history and physical examination, routine laboratory tests, chest radiography, abdominal ultrasonography, esophago-gastroduodenoscopy (EGD), and nutritional and psychiatric assessment. Additional examinations or specialist consultations were performed when clinically necessary. Furthermore, patients underwent preoperative HRM, 24-hour pH monitoring, and GERD symptom evaluation by means of the GERD-HRQL questionnaire. Reported use of proton pump inhibitors (PPIs) or other antacid medications was recorded.

One patient was dropped out of the study, although asymptomatic, because of the extremely severe GERD signs found during the preoperative workup and underwent an RYGB; 1 patient did not complete follow-up because she was found to have a gastric adenocarcinoma at the level of the incisura angularis during the 1-year postoperative EGD and was submitted to neoadjuvant chemotherapy.

Follow-up was fully completed at least 1 year post operation (mean follow up, $14.3 \pm 2.1 \text{ mo}$) by 19 patients and comprised physical examination, routine laboratory tests, EGD, HRM, 24-hour pH monitoring, and GERD symptom evaluation by means of GERD-HRQL questionnaire.

Patient inclusion criteria comprised those enlisted by international guidelines [8]. Patients were included in the study regardless of preexisting GERD symptoms or antacid and/or PPI medication use. Patients were excluded from the study if they had HH $>2 \text{ cm}$, previous gastrointestinal surgery, evidence of grade B–D EE and evidence of BE on preoperative EGD.

The study was approved by the Ethical Committee of this University hospital. All participants provided written informed consent to participate in the study. Additional written informed consent was obtained before all surgical procedures.

Sample size calculation

Given that the accrual phase of the study a was 15 months and the follow-up time f was 12 months, using the exact chi-square distribution and assuming the Weibull shape parameter $\beta = 1.5$, the sample size would have been 17 with a power of .80 and a significance of .05. With an attrition rate of .20, the number of participants to enroll in our study was 21 [9].

Endoscopy

EGD was performed by using a high-definition standard gastroscope (Evis ExeraII; Olympus Corporation, Shinjuku, Tokyo, Japan) under conscious sedation (intravenous midazolam). The distance from the upper incisors to the Z-line (squamous-columnar junction) and to the diaphragmatic esophageal hiatus were measured. An upward migration of the Z-line $\geq 2 \text{ cm}$ (i.e., intrathoracic migration of the gastric sleeve) was considered noteworthy and recorded.

Esophageal inflammatory lesions were classified according to the Los Angeles Classification [10]. Biliary-like reflux into the esophagus and cardiac continence were also recorded. Cardiac incontinence was evaluated during the retroflexion maneuver and was defined by a wide-open cardia allowing the passage of gastric fluid content into the esophagus.

High-resolution manometry

Patients using drugs that might influence esophageal motility (e.g., tricyclic antidepressants, calcium channel blockers, anticholinergic, prokinetic drugs) were advised to discontinue them for at least 7 days before the study.

HRM with esophageal pressure topography was carried out using a 4.7-mm water-perfused catheter with 26 open tips positioned at 1-cm intervals (EB Neuro S.p.A. Firenze). The catheter was perfused with distilled water at a rate of .15 mL/min by a low-compliant pneumohydraulic infusion system. The catheter was positioned transnasally, and during insertion the 2 high-pressure areas, represented by the upper and lower esophageal sphincters, were visualized on the monitor after a 30-second period of basal recording.

The study was performed in supine position, after an observation period of dry swallows and included the administration of at least 10 (5 mL) water swallows every 20 seconds and a 5-minute period to assess the basal sphincter pressure. A solid bolus was also administered if the first test did not cause alterations of the esophageal manometric pattern regardless of subjective patient symptoms. HRM parameters were analyzed for each peristaltic wave, and manometric dysmotilities were classified according to the Chicago Classification [11]. Data were analyzed using a dedicated software (Gastro Explorer EB Neuro S.p.A. Firenze).

In particular, the following parameters were analyzed: esophagogastric junction (EGJ) basal pressure, deglutitive LES relaxation, peristaltic activity, and peristaltic wave vigor. Additionally, for each liquid swallow the following were calculated: average distal contractile integral (DCI) (reference range: 450–8000 mm Hg/s/cm), average basal LES pressure (10–40 mm Hg), distal latency (DL) (>4.5 s), and LES average integrated relaxation pressure (<15.0 mm Hg).

Twenty-four-hour pH monitoring

The study was performed on an outpatient basis with the removal of the catheter after 24 hours. Patients were kept nil orally for at least 12 hours before the examination. PPIs were discontinued for at least 7 days before the study, and antacid medications were interrupted for at least 3 days prior. During pH monitoring, patients were told not to modify their diet habits and to keep a diary record of their food consumption, supine or standing position, and any other relevant symptom or complaint.

Esophageal pH was measured using a 2-mm probe with 2 antimony pH electrodes placed at a distance of 20 cm (proximal electrode) and 5 cm (distal electrode) above the LES. The pH measurement range was $7.01 \pm .05$ to $1.01 \pm .05$. The pH catheter probe was positioned transnasally. A portable data storage device with 2 channels (Medtronic Digitrapper pH-Z Testing System) was used to record results.

Reflux episodes were calculated according to the DeMeester score system. (DeMeester score reference ranges: normal ≤ 14.7 , mild GERD = 14.7–50, moderate GERD = 51–100, and severe GERD >100). A rapid drop of esophageal pH ≤ 4 was considered as evidence of reflux. The episode of reflux was regarded as terminated when there was an increase back to a value of pH ≥ 4 . Reflux phases during the supine and upright position were measured independently.

The following parameters were especially considered: total reflux time at pH <4, percentage time of reflux in orthostatic or clinostatic position, total number of reflux episodes, number of reflux episodes >5 minutes, longest reflux episode, and DeMeester score. Registration percentages were calculated as time over 24 hours.

GERD-HRQL questionnaire

All patients completed a GERD-HRQL questionnaire preoperatively and 1 year postoperatively. It consists of a self-rating questionnaire encompassing 15 questions that specifically consider GERD symptoms experienced by the patient in the previous 2 weeks. Each question has a score from 0 (absence of symptoms) to 5 (severe symptoms), based on the frequency of symptoms and its interference with daily activities. The questionnaire examines characteristics of heartburn (items 1–6), swallowing (items 7 and 8), use of PPIs (item 9), and regurgitation (items 10–15). One final question investigates patient satisfaction with the present condition (item 16) but is not included in the final score. The total score ranges from 0–75 [12].

Surgical technique

Our standard surgical procedure has been previously described [13]. Full mobilization of the gastric fundus with complete dissection of the posterior gastric wall from the left diaphragmatic crus is achieved. The crural region is routinely explored to rule out the presence of hiatal hernias overlooked during endoscopy. A 48-Fr calibration orogastric bougie is routinely used. Resection is begun approximately 6 cm from the pylorus and continued cephalad reaching the angle of His. A gastric sleeve with a residual capacity of 60–80 mL (as measured by administration of methylene blue saline solution via a nasogastric tube) is achieved. Patients are started on a soft diet 3 days post operation and this is maintained for 30 days. PPI treatment is

prescribed for the first 5 months after surgery and is discontinued if the patient is asymptomatic for GERD.

Statistical analysis

Continuous variables are expressed as mean \pm SE for parametric data. Normality was assessed by Shapiro-Wilk test and visual examination of the distribution of the data. Nonparametric data were converted to log-scale for further analysis. Wilcoxon test was used to compare variables before and after SG. A P value $\leq .05$ was considered statistically significant. Linear regression analyses were performed and results are presented as β coefficients with 95% CI.

Pearson correlation coefficient are used to determine significant correlation.

The correlation between baseline total GERD-HRQL questionnaire score and baseline BMI was predicted by a quadratic equation: $ax^2 + bx + c = 0$, where x is the BMI at time 0 and the values of x , which are the solutions of the equation, are given by: $x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$

A binary logistic regression was used to predict presence or absence of Z-line upward migration 1 year after SG using DCI values at baseline as covariate.

HRM, DL, and DeMeester score at baseline were used as covariates in a multinomial logistic regression model with development of erosive esophagitis (EE) at 1-year follow-up as a dependent variable. Bootstrapping was used to estimate parameters and SEs [14].

We first ran univariate analyses to find the relation of the outcome with each predictor, 1 at a time, and then used only

Table 1

Demographic data, weight outcomes, 24-hr pH monitoring, high-resolution manometry, endoscopic findings, and GERD-HRQL questionnaire score results at baseline and 1 yr after SG

Variables	Preoperation	Post operation	P value
Sex (M/F)	4/15	NA	NA
Age, yr	41.6 \pm 2.8	NA	NA
Weight, kg	118.7 \pm 4.6	76.8 \pm 2.7	<.001
BMI, kg/m ²	41.2 \pm .9	26.8 \pm .8	<.001
Δ BMI (kg/m ²)	NA	14.4 \pm .9	NA
TWL, %	NA	34.8 \pm 1.7	NA
EWL, %	NA	71.3 \pm 3.6	NA
24-hr pH monitoring			
Total no. of reflux episodes, n	78.8 \pm 33.9	40.7 \pm 9.8	NS
No. of reflux episodes >5 min, n	3.9 \pm 1.8	2.9 \pm .9	NS
Longest reflux episode, min	58.5 \pm 30.7	12.5 \pm 3.6	NS
Total time of acid reflux with pH <4, %	10.7 \pm 5.6	4.4 \pm 1.1	NS
Total time of acid reflux in upright position, %	10.5 \pm 5.1	4.8 \pm 1.6	NS
Total time of acid reflux in supine position, %	10.2 \pm 5.6	3.4 \pm 1.2	NS
DeMeester score	23.1 \pm 7.5	22.8 \pm 5.8	NS
High-resolution manometry			
LESP, mm Hg	17.1 \pm 3.7	15.8 \pm 2.9	NS
IRP, mm Hg	4.68 \pm .9	3.9 \pm .7	NS
DCI, mm Hg/s/cm	2772.8 \pm 399.9	2060.4 \pm 338.9	.0016
DL, s	6.4 \pm .4	6.9 \pm .6	NS
Endoscopy			
Z-line upward migration >2 cm, % (n)	31.6 (6)	84.2 (16)	<.001
Cardial incontinence, % (n)	26.3 (5)	73.7 (14)	.001
Biliary gastric stagnation, % (n)	5.3 (1)	47.4 (9)	<.001
Esophageal mucosal tongues, % (n)	5.3 (1)	42.1 (8)	.002
Erosive esophagitis, % (n)	10.5 (2)	42.1 (8)	.01
Grade A	10.5 (2)	26.3 (5)	NA
Grade B	NA	15.8 (3)	NA
Grade C	NA	NA	NA
Grade D	NA	NA	NA
PPI intake, % (n)	10.5 (2)	42.1 (8)	.02
GERD-HRQL score	7.9 \pm 2.7	11.4 \pm 3.3	NS

GERD-HRQL = Gastroesophageal Reflux Disease Health-Related Quality of Life; M = male; F = female; NA = not applicable; BMI = body mass index; Δ BMI = change in body mass index; TWL = total weight loss; EWL = excess weight loss; NS = not significant; LESp = lower esophageal sphincter pressure; IRP = integrated relaxation pressure; DCI = distal contractile integral; DL = distal latency; PPI = proton pump inhibitor.

Data are presented as mean \pm SE or percentage (n) of patients.

those variables meeting a preset cutoff of $P < .05$ in the multinomial model.

Multicollinearity was excluded when the variance inflation factor was between 1 and 10.

Data analysis was performed in SPSS version 25 (IBM, Armonk, NY).

Results

Table 1 reports mean \pm SE of weight outcomes, variables of HRM, 24-hour pH monitoring, endoscopic findings, and GERD-HRQL questionnaire score at baseline and 1 year after SG. The scores for each single item of the GERD-HRQL questionnaire are reported in Supplementary Table 1.

A total of 19 patients, 15 (78.9%) female and 4 (21.1%) male, of mean age 41.6 ± 2.8 years and BMI of $41.2 \pm .9$ kg/m², completed the present study. BMI change was $14.4 \pm .9$ kg/m² ($P < .001$), with a % total weight loss of $34.8\% \pm 1.7\%$. No postoperative major and minor complications or mortality were registered during this study.

The number of participants taking PPIs increased significantly ($P = .02$) from 10.5% at baseline to 42.1% 1 year after SG. No significant changes were observed in the single item and total score of the GERD-HRQL questionnaire (Supplementary Table 1).

The preoperative DeMeester score was 23.1 ± 7.5 , indicating mild GERD, which did not change significantly after surgery (22.8 ± 5.8 , $P = .978$). Additionally, 2 patients were diagnosed as having markedly severe GERD based on the preoperative 24-hour pH monitoring (baseline DeMeester score = 274 and 498). In both patients, all pH-metric variables significantly improved after SG ($P = .0005$), reaching a postoperative DeMeester score of 13.1 and 3.8, respectively, thus configuring a normal result, negative for GERD. Overall, the variables of the 24-hour pH monitoring did not change significantly after SG. However, a reduction tendency of acid reflux, as shown by the decrease in the number of total reflux episodes, the number of reflux episodes >5 minutes, the longest reflux episode, and the exposure to acid in upright and supine position after SG can be noted (Table 1).

None of the HRM variables changed significantly, except for DCI, which decreased from 2772.8 ± 399.9 mm Hg/s/cm to 2060.4 ± 338.9 mm Hg/s/cm ($P = .016$), indicating a reduction in peristaltic vigor of the esophageal smooth muscle. No patients pre- or postoperatively had values indicating esophageal hypercontractility (i.e., DCI >8000 mm Hg/s/cm), while 2 patients had DCI <450 mm Hg/s/cm preoperatively, and 4 patients had a DCI <450 mm Hg/s/cm 1 year after surgery, signifying an increase in weak esophageal peristalsis.

Endoscopic findings showed significant changes after SG, with an increase in the number of cases of cardiac incontinence (from 26.3% to 73.7%, $P = .001$), erosive esophagitis (from 10.5% to 42.1%, $P = .01$), Z-line upward migration

>2 cm (from 31.6% to 84.2%, $P < .0001$), and biliary gastric stagnation (from 5.3% to 47.4%, $P < .0001$) and appearance of esophageal mucosal tongues (from 5.3% to 42.1%, $P = .002$).

DL at baseline significantly ($R^2 = .37$, $P = .020$) predicted the DeMeester score at 1 year after SG: for each unit increase of DL there was 7.2 increase of the DeMeester score (Fig. 1).

BMI at baseline was significantly correlated with the baseline GERD-HRQL questionnaire total score in a U-shaped curve manner, showing that those patients with a BMI <40 kg/m² had a higher GERD-HRQL questionnaire total score (Fig. 2).

The logistic regression significantly ($P = .028$) predicted the development of Z-line upward migration at 1-year follow-up according to the equation:

$$\text{Logit (Z-line upward migration at T1)} = -2.503 + .001 \cdot \text{DCI at T0}$$

The confidence interval for $\text{EXP}(\beta)$, where β is the coefficient of DCI at baseline, was 1.000 to 1.002, indicating that the presence of DCI at baseline is between 1.000 and 1.002 times as likely to induce Z-line upward migration postoperatively. Thus, we found that DCI values at baseline predict a Z-line upward migration at 1 year after SG. The higher the DCI the higher the probability of developing postoperative Z-line upward migration. After SG, DCI significantly decreased (Table 1). The model predicted correctly the classification of Z-line upward migration at 1 year after SG, assigning it correctly in 87.5% of cases (12.5% false-negative error) and its absence in 100% of cases.

HRM, DL, and DeMeester score at baseline predicted the development of EE at follow-up, as shown by the bootstrap estimates of a logistic regression model with EE at 1 year after SG as a dependent variable (Table 2). The model assigned a correct probability to develop EE in 71.4% of

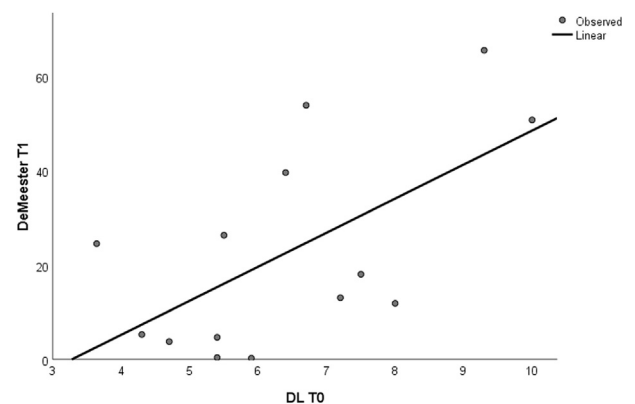


Fig. 1. Distal latency at baseline significantly ($R^2 = .37$, $P = .020$) predicts the DeMeester score at 1 yr after SG: for each unit increase of DL there was 7.235 increase of the DeMeester score. T1 = 1 yr post operation; DL = distal latency; T0 = baseline.

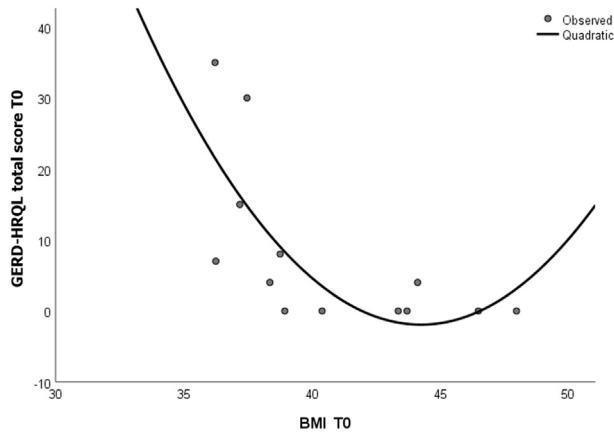


Fig. 2. BMI at baseline is significantly correlated with the baseline GERD-HRQL questionnaire total score in a U-shaped curve manner, showing that those patients with a baseline BMI <40 kg/m² had a higher HRQL questionnaire total score. GERD-HRQL = Gastroesophageal Reflux Disease Health-Related Quality of Life; BMI = body mass index; T0 = baseline.

cases and the absence of EE in 77.8% of cases with 22.2 and 28.6 % of false-negatives, respectively.

Discussion

Data in literature regarding the relation between GERD and SG are still rather conflicting. Reflux symptoms after

this procedure are reported to be improved in some studies [15,16] but worsened in others [17–20]. The so-called “antireflux barrier” is based on the correct disposition of several anatomic structures that compose it. During SG a modification of part of those structures are able to promote or worsen gastroesophageal reflux [21]. In fact, after SG several mechanisms have been proposed as responsible factors of GERD and include the absence of the gastric fundus with abolition of the angle of His, increased intraluminal pressure, division of sling fibers and/or phrenoesophageal ligament causing decreased LES pressure, antral pump loss due to a radical resection of the antrum, middle gastric stricture with delayed gastric emptying, and HH with intrathoracic migration of the gastric sleeve [7].

Several investigations have been conducted in this regard and have sought to find a correlation between reported symptoms and actual esophageal damage because it is known that the continuous acid and bile reflux damages the esophageal mucosa, leading to a structural modification of the stratified squamous epithelial cells that are replaced by intestinal columnar cells (i.e., intestinal metaplasia) [22–24].

Most short-term studies have not detected de novo GERD but on the contrary report an improvement of reflux symptoms. This initial effect might perhaps come as a result of

Table 2

HRM, DL, and DeMeester score at baseline (T0) predict postoperative (T1) erosive esophagitis at follow-up, as shown by the bootstrap estimates of a logistic model with erosive esophagitis at 1 yr after SG as a dependent variable

Bootstrap* for variables in the equation						
Variables	β	Bias	SE	Sig. (2-tailed)	95% CI for EXP(β)	
					Lower	Upper
HRM (T0)	3.974	52.251 [†]	1719.802 [†]	.025 [†]	–211.685 [†]	1011.565 [†]
LESP (T0)	.049	.385 [†]	4.950 [†]	.094 [†]	–7.883 [†]	10.475 [†]
IRP (T0)	–.175	–4.159 [†]	24.630 [†]	.097 [†]	–44.186 [†]	28.243 [†]
DCI (T0)	.001	.009 [†]	.185 [†]	.090 [†]	–.110 [†]	.096 [†]
DL (T0)	–.800	–8.277 [†]	124.019 [†]	.008 [†]	–103.000 [†]	123.457 [†]
DeMeester (T0)	–.030	–3.010 [†]	30.093 [†]	.030 [†]	–56.534 [†]	2.254 [†]
Constant	2.128	41.760 [†]	878.194 [†]	.154 [†]	–482.011 [†]	841.615 [†]

Classification table [‡]			
Observed	Predicted		Percentage correct
	Erosive esophagitis (T1)		
	0	1	
Erosive esophagitis (T1)			
0	7	2	77.8
1	2	5	71.4
Overall percentage			75.0

HRM = high-resolution manometry; DL = distal latency; T0 = baseline; T1 = 1 yr post operation; SG = sleeve gastrectomy; β = unstandardized regression weight; Sig. = significance; EXP(β) = exponentiation of the β coefficient; LESP = lower esophageal sphincter pressure; IRP = integrated relaxation pressure; DCI = distal contractile integral; DL = distal latency.

The model assigned a correct probability of developing erosive esophagitis in 71.4% of cases and the probability of not developing it in 77.8% of cases.

* Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples.

[†] Based on 630 samples.

[‡] Cut value is .500.

the substantial weight loss, which causes in turn a reduction of intraabdominal pressure [25].

A prospective study by Sharma et al. [26] analyzing the effects of SG on GERD by means of questionnaires, endoscopy, and radionuclide scintigraphy before and 12 months after surgery found there actually was an overall improvement of GERD. The Carlsson Dent Score and Severity Score both revealed a significant decrease of GERD symptoms postoperatively ($P < .05$). Furthermore, the severity of esophagitis declined, even though the radionuclide scintigraphy demonstrated a visibly significant increase of GERD (6.25% versus 78.1% post operation) ($P < .001$). Authors conclude that in consideration of such findings, GERD is not to be considered as a contraindication to SG, although long term follow up is advisable.

Rebecchi et al. [15] performed a prospective clinical trial on 65 patients 2 years after SG by using symptom questionnaires, HRM, and 24-hour pH monitoring. Patients were divided into 2 groups according to results of the preoperative 24-hour pH monitoring. Symptoms, DeMeester score, and total acid exposure improved in the group of patients with a pathologic preoperative 24-hour pH monitoring ($P < .001$), which was similar to our results. De novo GERD was present in only 5.4% of those patients with a normal 24-hour pH monitoring.

Two further studies comparing the effects of both SG and RYGB on postoperative GERD in the short-term, by means of symptomatic assessment, functional investigations (i.e., HRM, 24-h pH monitoring, barium swallow), and endoscopy, confirmed how the development of postoperative GERD was significantly greater in SG than in patients who underwent RYGB, suggesting that SG should be contraindicated in those patients already presenting with reflux symptoms at baseline and that extensive counseling explaining all possible reflux-related consequences should be performed before an SG procedure [27,28].

Mid- to long-term studies, on the other hand, suggest that the development of GERD after SG should be considered as an expected collateral effect of variable degree.

A large retrospective database review by DuPree et al. [17], involving 4832 patients, compared the effects of SG and RYGB on known preexisting GERD. The vast majority of SG patients (84.1%) maintained GERD symptoms also postoperatively, while 15.9% had a symptomatic resolution. Patients who were asymptomatic for GERD developed symptoms in 8.6% of cases after SG. In contrast, RYGB led to GERD remission in 62.8% of patients by 6 months from surgery. Furthermore, the SG group required a higher rate of revisional bariatric surgery (.6% versus .3%, $P < .05$) and had worst weight loss results. Because of such unfavorable outcomes, authors advocate that preoperative GERD might represent a relative contraindication to SG.

Our group also published a prospective study involving 110 patients undergoing SG in which the incidence of GERD was analyzed based on clinical, endoscopic, and

histologic findings. EGD primarily showed the presence of an upward migration of the Z-line and a biliary-type reflux in 81(73.6%) and 82 patients (74.5%), respectively. Furthermore, a statistically significant worsening of the severity of EE was observed, and nondysplastic BE was diagnosed in as many as 17.2% of patients. No significant correlation was found between GERD symptoms and endoscopic findings [21].

Following such reports, several authors further investigated this alarming precancerous condition observed after SG, and a recent multicenter prospective study, performing systematic EGD in 90 consecutive patients 5 years after SG, reported a prevalence of BE as high as 18.8% [29].

Finally, a recent systematic review and meta-analysis by Yeung et al. [30], appraising all current literature reporting the incidence of GERD and its correlated sequelae after SG, found substantially elevated rates of de novo GERD in 20%, in addition to the appearance of EE and BE in 28% and 8%, respectively. This study, however, pointed out a high heterogeneity regarding the method of GERD evaluation and definition, with a minority of studies actually implementing functional assessments. Nevertheless, those studies using functional and invasive methods of investigation actually found a higher incidence of reflux than those analyzing symptoms alone.

The strength of the present study is that of combining a complete and prospective analysis through the assessment of different objective and functional viewpoints, implementing an endoscopic, manometric, and pH-metric evaluation before and approximately 1 year after SG. From a pH-metric point of view, we found an overall reduction tendency of the number of total reflux episodes, the number of reflux episodes >5 minutes, and the exposure to acid in upright and supine position and a stability of the DeMeester score at 14.3 ± 2.1 months after surgery. This reduction, although not statistically significant, is possibly attributable to the resection of the gastric fundus that leads to a drop in acid secretion, which can explain the greater pH registered during the examination. The lack of change in DeMeester score might also be in part associated with the marked increase of PPI use after SG, although all patients were required to discontinue all gastric antisecretory medications at least 7 days before the study. Moreover, 2 patients with a markedly severe GERD at baseline (DeMeester score = 274 and 498) had a significant improvement of all pH-metric parameters after SG ($P = .0005$), reaching a postoperative DeMeester score of 13.1 and 3.8, respectively, thus configuring a normal result, negative for GERD. These results may suggest an etiology different from acid reflux. In fact, this outcome is also corroborated by the endoscopic findings, which have highlighted the presence of a prevalently biliary gastric stagnation ($P < .001$). Acid reflux in our cohort of patients approximately 1 year after SG seems diminished (Table 1), validating the hypothesis that the esophageal sequelae detected during endoscopy might be

caused by a biliary-type reflux, as opposed to an acidic one, to which patients are exposed post SG.

The pre- and postoperative HRM results can be considered largely superimposable, with the exception of DCI values. DCI decreased from 2772.8 ± 399.9 mm Hg/s/cm to 2060.4 ± 338.9 mm Hg/s/cm ($P = .016$), indicating a significant reduction in peristaltic vigor of the esophageal smooth muscle. This allows inference that contrary to available published data [31,32], SG is not likely responsible for causing an increased intragastric pressure or esophageal distmotility. In fact, from the present results, SG seems to lead to a decrease in the energy and potency of peristaltic esophageal waves required for the progression of the intraluminal bolus toward the gastric sleeve. Notably, the LES pressure remained unchanged after SG and no evidence of esophageal body abnormal motility was found on the postoperative HRM.

Furthermore, by using a logistic model with classical approach and bootstrap simulations, we found that DCI values at baseline predict a Z-line upward migration at 1 year after SG. The higher the DCI, the higher the probability of developing a significant postoperative Z-line upward migration. The model correctly predicted the development of a Z-line migration at 1 year in 87.5% of cases (12.5% false-negative error) and its absence in 100% of cases. Similarly, HRM, DL, and DeMeester score at baseline predicted the development of EE at follow-up. The model assigned a correct probability to develop EE in 71.4% of cases and its absence in 77.8% of cases with 22.2% and 28.6% false-negatives, respectively. This highlights the importance of performing a preoperative HRM in patients undergoing SG because it can help stratify the risk of developing EE and Z-line upward migration with a high accuracy and reliability.

Endoscopic results showed a substantially pejorative variation of all analyzed parameters. We found a significantly worsened cardinal incontinence ($P = .001$) and an overall substantial increase in the length of Z-line upward migration ($P < .001$) in as many as 84.2% of patients, with a de novo appearance of Z-line upward migration in 56.3% or an increase of its preexisting length in 37.5%. In 42.1% of the study group, we found the presence of gastric mucosal tongues at esophageal level post operation ($P = .002$). Also, the increased incidence of EE after SG was statistically significant, affecting 42.1% of patients ($P = .01$): 26.3% had a grade A esophagitis and 15.8% had a grade B esophagitis according to the Los Angeles Classification. No evidence of more severe grades of EE or BE were recorded in the present cohort of patients, and this might be attributable to the relatively short follow-up after surgery.

From a clinical point of view, patients reported through the GERD-HRQL questionnaire a slight but not statistically significant increase in the presence of reflux symptoms such as heartburn, regurgitation, dysphagia, and medication use (from 7.9 ± 2.7 to 11.4 ± 3.3 , $P = .5$). GERD-HRQL-related

symptoms had no correlation with endoscopic findings, further corroborating our previously published data [33].

Overall, SG modifies the mechanisms regulating gastroesophageal reflux. The intrathoracic migration of the proximal portion of the gastric sleeve, present in 84.2% of our study group, might contribute to the reduction of the pressure gradient between the EGJ, with migration into the mediastinum (low pressure) and the residual stomach in the abdomen (high pressure) promoting GERD. Another fundamental factor to take into account is the composition of refluxate. The pH-metric data demonstrated that the refluxate is mainly mixed or biliary, which brings intragastric pH to higher levels than patients who did not undergo SG. This could explain the lack of correlation between symptoms and endoscopic findings and the relative ineffectiveness of PPI treatment in such patients.

Limitations

Some limitations to this study must be acknowledged. The short-term follow-up might affect results, especially for histologic modifications, which may require longer periods of time to take place. The number of patients included in the study is limited and might be attributable to the invasive nature of the implemented examinations, such as 24-hour pH monitoring and HRM, which decrease the compliance of patients to follow-up. Another limitation is the lack of esophageal impedance monitoring, which could have allowed the detection of nonacid reflux. However, to further corroborate and confirm our present findings, we are in the process of performing esophageal impedance monitoring to better record nonacid reflux in a new study protocol.

Conclusions

The emerging data from the present study confirm the effectiveness of SG in terms of rapid and substantial weight loss in conjunction with a low rate of complications. It clearly appears that modifications of the physiopathologic mechanisms in gastroesophageal reflux regulation take place after this surgical procedure. In particular, we have reported a worsening of GERD symptoms, with a significant increase in PPI intake and the development of abnormal endoscopic findings, including EE, appearance of esophageal mucosal tongues, upward Z-line migration, and a reduction in the peristaltic vigor of the esophagus. Additionally, we highlight the importance of performing a preoperative HRM in patients undergoing SG because it can help stratify the risk of developing EE and Z-line upward migration after SG with a high accuracy and reliability. The combined analysis of these outcomes seems to indicate a different etiopathogenesis of the abnormal endoscopic esophageal lesions and GERD symptomatology reported by patients postoperatively, which is not likely caused by an acid-type reflux. The presence of biliary gastric

stagnation registered in a high percentage of patients during endoscopy could play a relevant role in such mechanisms. An accurate preoperative endoscopy is of paramount importance for a correct patient selection, and postoperative endoscopic surveillance should be encouraged regardless of the presence or absence of symptoms.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.soard.2020.07.013>.

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