TITLE: Esophagogastric junction morphology is associated with a positive impedance-pH monitoring in patients with GERD

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ABBREVIATIONS:

AET, acid exposure time; **CD**, crural diaphragm; **EGJ**, esophagogastric junction; **ERD**, erosive reflux disease; **GERD**, gastroesophageal reflux disease; **HRM**, high resolution manometry; **LES**, lower esophageal sphincter; **MII-pH**, multichannel intraluminal impedance pH monitoring; **NERD**, non-erosive reflux disease; **SAP**, symptom association probability; **SI**, symptom index.

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AUTHOR CONTRIBUTION

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ABSTRACT

Background High-resolution manometry (HRM) provides information on esophagogastric junction (EGJ) morphology, distinguishing three different subtypes. Data on the correlation between EGJ subtypes and impedance-pH detected reflux patterns are lacking. We aimed to correlate the EGJ subtypes with impedance-pH findings in patients with reflux symptoms.

Methods. Consecutive patients with suspected gastroesophageal reflux disease (GERD) were enrolled. All patients underwent HRM and impedance-pH testing off-therapy. EGJ was classified as: Type I, no separation between the lower esophageal sphincter (LES) and crural diaphragm (CD); Type II, minimal separation (>1 and <2 cm); Type III, !2 cm separation. We measured esophageal acid exposure time (AET), number of total reflux episodes and symptom association analysis. Key

Results. We enrolled 130 consecutive patients and identified 46.2% Type I EGJ, 38.5% Type II, and 15.4% Type III patients. Type III subjects had a higher number of reflux episodes (61 vs 45, $p < 0.03$, vs 25, $p < 0.001$), a greater mean AET (12.4 vs 4.2, $p < 0.02$, vs 1.5, $p < 0.001$) and a greater positive symptom association (75% vs 72%, $p = 0.732$ vs 43.3%, $p < 0.02$) compared with Type II and I patients, respectively. Furthermore, Type II subjects showed statistically significant (overall $p < 0.01$) increased reflux when compared with Type I patients. Type III and II EGJ morphologies had a more frequent probability to show a positive multichannel intraluminal impedance pH monitoring than Type I (95% vs 84% vs 50%, $p < 0.001$).

Conclusions & Inferences. Increasing separation between LES and CD can cause a gradual and significant increase in reflux. EGJ morphology may be useful to estimate an abnormal impedance-pH testing in GERD patients.

Keywords. esophagogastric junction, GERD, high-resolution manometry, impedance monitoring.

INTRODUCTION

Esophagogastric junction (EGJ) is the main defense against gastroesophageal reflux. Anatomically EGJ is constituted by the lower esophageal sphincter (LES) and by the crural diaphragm (CD). The intrinsic muscles of the distal esophagus together with the sling fibers of the proximal stomach constitute the LES, while CD is composed by muscular bands that emerge from the anterior longitudinal ligaments over the upper lumbar vertebrae and form two ribbon-like bundles diverging and crossing each other like a scissor. The lateral fibers of each hiatal limb insert into the central tendon of the diaphragm and collaborate with phreno-esophageal membrane into maintaining fixation of the EGJ to the diaphragm.(1,2)

Esophagogastric junction competence depends on the integrity and interaction between all these elements. Reflux of gastric juice into the esophagus is otherwise due to EGJ dysfunction, with a strict correlation between the multitude and magnitude of endangerment of EGJ constituent elements and the severity of gastroesophageal reflux disease (GERD). High-resolution manometry (HRM) is characterized by a higher number of pressure recording sites and a lower distance between them compared with traditional manometry. This allows to evaluate separately CD and LES contractions and their anatomical relationship. According to Chicago classification, we can even distinguish three subtypes of EGJ based on the separation between CD and LES.(3) In a recent study by Pandolfino et al., impairment of CD function to increase inspiratory EGJ pressure resulted to be the only independent predictor of GERD using logistic regression analysis. When patients were examined according to EGJ subtypes, the authors observed that type III EGJ patients, corresponding to an axial LES-CD separation >2 cm, presented a higher proportion of erosive esophagitis (EE) or non-erosive reflux disease (NERD) compared with controls and functional heartburn patients diagnosed according to pH-monitoring and upper endoscopy aspects and that, on the other hand, less than 5% of controls or functional heartburn presented type III EGJ.(4) In a previous study by Bredenoord et al., CD-LES separation resulted into a twofold increase in acidic and weakly acidic reflux measured with 90 min postprandial HRM and impedance-pH monitoring.(5) To date, data on the correlation between EGJ subtypes and 24-h impedance-pH monitoring are lacking.

The aim of this study was to correlate the different EGJ subtypes with 24-h impedance-pH findings in patients with symptoms of GERD.

METHODS

Subjects

We prospectively enrolled consecutive patients referred to four different outpatient motility laboratories in Italy (Academic Hospital of Padua, Naples, Genoa and Pisa) between March 2013 and January 2014 and presenting typical GERD symptoms (e.g., heartburn and regurgitation) lasting more than 6 months and occurring at least three times per week. The study protocol was approved by the local Internal Review Boards and performed according to the Declaration of Helsinki. All patients gave written informed consent before the start of the study. At first visit, demographics (with recording of height and weight), current medications, tobacco use, and alcohol consumption, clinical history, and previous instrumental investigation were reviewed and recorded. A structured questionnaire on gastroesophageal reflux symptoms was administered.(6) The exclusion criteria were: a history of thoracic, esophageal, or gastric surgery; primary or secondary severe esophageal motility disorders (e.g., achalasia, scleroderma, diabetes mellitus, autonomic, or peripheral neuropathy, and myopathy); the use of nonsteroidal anti-inflammatory drugs and aspirin; pregnancy; the presence of peptic stricture or duodenal or gastric ulcer on upper endoscopy; and the inability to pass through the EGJ. All subjects who agreed to participate in our study underwent upper endoscopy, HRM and impedance-pH monitoring. The patients were asked to discontinue any medication that would influence esophageal motor function 5–7 prior to motility testing, whereas patients treated with antisecretory drugs were asked to discontinue acid-suppressive therapy at least 30 days before the start of reflux monitoring. During the washout period, the patients were allowed to use an antacid or alginate, on as needed basis, for the relief of heartburn.(7)

Upper endoscopy.

Upper gastrointestinal endoscopy was performed according to international guidelines. The EGJ was defined as the level at which the tubular esophagus joined the proximal margin of gastric folds. The squamocolumnar junction was defined as the point where the normal squamous epithelium joined the pink mucosa of the columnar-lined esophagus. Esophagitis was staged according to the Los Angeles classification, Barrett's esophagus was defined as a detectable upward displacement of the squamocolumnar junction at endoscopy, confirmed by intestinal metaplasia at histology.(8,9)

High-resolution manometry.

Esophageal pressure topography studies were done with a 4.2 mm outer diameter solid-state assembly with 36 circumferential sensors spaced at 1-cm intervals (Given Imaging, Los Angeles, CA, USA).

Before recording, transducers were calibrated at 0 and 300 mmHg using externally applied pressure. Examinations were done in a supine position after at least a 6-h fasting period and the manometric assemblies were positioned with at least five intragastric sensors. The manometric protocol included a 5-min baseline recording to assess the EGJ and at least 10 single water swallows (5 mL) at 30-s intervals to evaluate the esophageal peristalsis.(10)

Data acquisition, display, and analysis were performed using dedicated software (Manoview analysis software; Given Imaging, Duluth, GA, USA), after a proper thermal compensation. Lower esophageal sphincter was localized and its pressure and relaxations (using the integrated relaxation pressure over 4 s) evaluated; proximal and distal borders were marked according to pressure difference related to intraesophageal and intragastric pressure marks. Crural diaphragm was marked as the axial level characterized by maximal inspiratory pressure augmentation. In individuals with normal anatomy, LES and CD were superimposed and indistinguishable. Patients were then classified to have three morphological types of EGJ, based on the presence of axial cranial separation between LES and CD, measured in cm, and classified as: Type I, no separation between the LES and the CD; Type II, minimal separation (>1 and <2 cm); Type III, ≥2 cm of separation.(4) Other parameters, which were measured, included the distal contractile integral and the distal latency as previous defined.(11) The individual swallow type was categorized and the diagnosis of the esophageal pressure topography plots was made according to the Chicago Classification v. 3.0.(12)

Esophageal impedance and pH monitoring.

Esophageal impedance- pH monitoring was performed off-therapy using an ambulatory multichannel intraluminal impedance (MII) and pH monitoring system (Sleuth; Sandhill Scientific, Inc., Highland Ranch, CO, USA). The methodology of probe calibration, catheter placement, patient instruction, and performance has been previously described.(13) On the monitoring day, each subject ate three standard meals of a Mediterranean diet, as previously reported.(14) Multichannel intraluminal impedance-pH data were collected and analyzed with the Bioview GERD Analysis Software (Sandhill Scientific Inc.). The following variables were assessed: distal esophageal acid exposure as percentage (%) of time (acid exposure time, AET) with pH <4 (abnormal if total time with pH <4 was greater than 4.2%), number and quality (acid, weakly acid, andweakly alkaline) of reflux detected at MII (normal value <54).

Analysis of correlation between reflux and reported symptoms was evaluated using symptom index (SI, positive if >50%) and symptom association probability (SAP, positive if >95%), as described elsewhere in details.15 Patients were classified having a positive MII-pH monitoring if at least one of the three parameters considered (total AET, total number of reflux events, SI and/or SAP) was abnormal. All HRM and MII-pH tracings were reviewed manually by two expert investigators (ES, ST), independently and in a blinded manner to ensure accurate detection and classification of EGJ morphology, motility, and reflux patterns. Any discrepancy in the assessment was further discussed and a consensus was reached. Meal periods were excluded from the analysis. These results have been previously reported in part in abstract form.(16,17)

Statistical analysis

Data were collected and analyzed using statistical software SPSS version 22 (Statistical Package for the Social Sciences, Chicago, IL, USA). Data for categorical variables are expressed as proportions and frequencies and data for continuous variables are expressed as median and interquartile (25–75th) range, unless otherwise specified. As data were not normally distributed, we used a nonparametric test (Mann–Whitney test) when comparing continuous parameters and Fisher's exact test was performed for comparison of categorical variables. Univariate and multivariate analysis were performed for testing the predictive potential of EGJ morphology in terms of positivity at impedance-pH monitoring. A two-sided p value of 0.05 was considered statistically significant.

RESULTS

We enrolled 130 (65M/65F; median age 53 [21–76]) consecutive patients with suspected GERD symptoms. At HRM, the study of LES-CD position allowed us to classify as Type I EGJ morphology 60 (46.2%) patients, as Type II EGJ 50 (38.5%) patients and as Type III EGJ 20 (15.4%). The three groups were matched for sex, but not for age. Indeed, patients with Type III EGJ were found to be older than patients with Type I and II EGJ ($p = 0.043$). The baseline characteristics of these individuals are shown in **Table 1**.

Endoscopy features and EGJ morphology

At upper endoscopy, 22 (16.9%) patients had EE (Grade A, n = 16, Grade B, n = 6), 10 (7.7%) had short-segment Barrett's esophagus and 98 (75.4%) had no mucosal breaks. In particular, Type I EGJ usually presented with no mucosal breaks (88.3%), with only 8.3% of patients having EE and only 3.3% bearing Barrett's esophagus. Type III, instead, showed a significant increase in EE and Barrett's esophagus (30% and 15%, respectively; $p < 0.01$) when compared with Type I EGJ. A statistical difference was reached also when comparing Type I to Type II EGJ, with an increase in EE and Barrett's esophagus (22% and 10%, respectively; $p < 0.02$).
When comparing Type II with Type III EGJ, the latter showed a higher prevalence of EE ($p < 0.02$).

Motility features and EGJ morphology

Based on Chicago Classification, the most frequent motility patterns were represented by normal peristalsis (75 patients, 57.7%), ineffective motility (30 patients, 23.1%), and fragmented peristalsis (11 patients, 8.5%). Absent peristalsis, outflow obstruction, jackhammer esophagus, and esophageal spasm were infrequent (0.8%, 3.8%, 1.5%, and 4.6%, respectively). Analyzing EGJ subgroups, Type I morphology showed a higher frequency of Normal motility (66.7%) than Type II (50%) and Type III (50%) and a lower rate of Ineffective motility (15%) than Type II and Type III morphology (30% and 30%, respectively). However, statistically significant differences were not reached among groups.

Reflux features and EGJ morphology

At MII-pH monitoring, patients with Type III EGJ had an higher median number of reflux episodes (61 [36–91] vs 45 [26–64], $p < 0.03$, vs 25 [19–43], $p < 0.001$, respectively), a greater mean AET (12.4 [3.9–25.1] vs 4.2 [1.8–9.7], $p < 0.02$, vs 1.5 [0.6–3.5], $p < 0.001$, respectively), and had more frequently a positive symptoms association (15 [75%] vs 36 [72%], $p = 0.732$, vs 26 [43.3%], $p < 0.02$, respectively) compared with patients with Type II and Type I EGJ (Figs 1–3). Moreover, patients with Type II EGJ tended to have a higher median number of reflux episodes, mean AET and a more frequently positive symptom association compared with patients with Type I EGJ ($p < 0.02$, $p < 0.05$ and $p < 0.02$, respectively). Re-reflux episodes were more frequent in patients with Type III EGJ compared to patients with Type II and Type I EGJ (27 [16–39] vs 14 [8–23], $p < 0.01$, vs 6 [4–11] $p < 0.001$), and this was true also for patients with Type II EGJ compared to patients with type I EGJ ($p < 0.01$). Overall, Type III and Type II had a more frequent probability to show a positive MII-pH than Type I EGJ (95%, $p < 0.001$, $r = 0.233$, CI: 0.079–0.511, vs 84% $p < 0.003$, $r = 0.242$, CI: 0.068–0.387; vs 50%, respectively; Fig. 4). Incidence of abnormal AET, or increased number of total reflux events or positive reflux-symptom association between distinct EGJ subgroups is shown in **Table 2**.

DISCUSSION

High-resolution manometry is currently the gold standard for evaluating esophageal motor function. In addition, this technique can offer interesting data about EGJ morphology, discriminating a possible axial separation between LES and CD. This event can be interpreted as the presence of hiatal hernia, or, more precisely, as an anatomical disruption of EGJ leading to a reduction in its physiological antireflux barrier activity. Our study confirms the hypothesis that, by increasing separation between LES and CD, patients have a gradual and significant rise of esophageal acid exposure and, as novel finding, of reflux episodes during the 24 h. Moreover, it highlights a direct relationship between EGJ morphology and symptoms perception as highlighted by the increased positive symptom correlation in patients with type III EGJ. Given the high sensitivity and specificity of HRM for hiatal hernia detection,(18) particularly in case of spatial LES-CD separation of 1.85 cm, these data emphasize the utility of performing EGJ assessment during manometry protocol and describing its morphology, in particular in patients undergoing reflux monitoring as preoperative assessment for endoscopic or surgical procedures. In 2007, Pandolfino et al. found a correlation between HRM characterizations of EGJ morphology with the objective demonstration of GERD.(4) All the patients underwent upper endoscopy and pH monitoring. According to presence/absence of endoscopic esophagitis and of decrease in pH at esophageal level, patients were classified into functional heartburn (endoscopy neg/pH neg), NERD (endoscopy neg/pH pos) and ERD (endoscopy pos/pH pos). Interestingly, mean LES-CD separation was similar between control subjects and functional heartburn patients, whereas NERD and ERD patients had significantly greater LES-CD separation. Furthermore, these authors found that end-expiratory EGJ pressure, LES-CD separation, and inspiratory EGJ augmentation were all significantly associated with GERD at logistic regression. This study is consistent with the above findings, highlighting a more frequent presence of a GERD when EGJ is disrupted. In particular, thanks to impedance monitoring, we were able to document for the first time that higher the LES-CD separation, higher the number of recorded refluxes is. In fact, Type III EGJ morphology patients had a statistically higher median number of total refluxes than Type II and Type I patients. It is likely that this disparity can be due to different mechanisms. The first hypothesis can be related to a drop in LES vigor; in fact, the lost contiguity with CD and the negative thoracic pressure can reduce the vigor of LES during the resting state, allowing a more frequent presence of transient LES relaxations (tLESRs). Secondly, the presence of a gastric portion through CD (i.e., hiatal hernia) can augment intraluminal pressure in the herniated segment and consequently, a higher rate of swallow-induced reflux is expected.

Bredenoord et al. have previously investigated 16 GERD patients with small hernias (<3 cm) by means of HRM and impedance monitoring, but only in the postprandial period.(5) These authors also

recorded the mobility of EGJ, further stratifying their study population by the presence of two distinct phases, a hernia state and a reduced state. Of note, they found significantly more frequent reflux episodes, detected by impedance-pH monitoring, during the hernia state (23.1±5.1 per hour) than in the reduced state (12.2±2.4 per hour). On the other hand, we decided to use the 24-h impedance monitoring to estimate the impact of EGJ morphology on reflux occurrence during the whole 24-h period. Moreover, 24-h impedance monitoring presents another advantage to note, when evaluating suspected GERD patients. In fact, in absence of impedance study, non-acid reflux remains undiagnosed and this underestimates GERD population in favor of functional heartburn.(19–22)
Our study, instead, correctly stratified subjects in negative GERD and positive GERD (considering positive those patients with at least one abnormal/positive parameter at impedance-pH monitoring, such as total reflux, total AET, or symptom association).(23) Currently, we confirmed that also acid exposure was augmented when an EGJ disruption was detectable. These data are in agreement with those reported by Pandolfino et al.(4) and with previous studies correlating the presence of hiatal hernia, assessed by concurrent fluoroscopy and manometry, with poor esophageal clearance and increased frequency of tLESRs.(24–27) Indeed, we found a decrease in incidence of normal peristalsis in favor of ineffective motility, even with no significant difference, which was recorded between Type I and Type II and III EGJ. In addition, we objectively demonstrated by means of the impedance technique that the increased esophageal acid exposure in patients with EGJ disruption may be also explained by the raised number of reflux episodes during the 24-h monitoring period. In particular, we found that the occurrence of re-reflux episodes (i.e., multiple reflux episodes occurring when pH is already below four and not detectable by pH-metry only) was more common in type III EGJ than in type II and I EGJ patients and between type II and type I EGJ patients. Finally, we correlated the increased esophageal acid exposure and the greater number of reflux episodes due to EGJ disruption in patients with type II and III EGJ with lack of mucosal integrity. Indeed, we found a statistically significant difference in frequency of ERD and Barrett's esophagus among our patients, with higher rate incidence in Type III and Type II than in Type I EGJ (30% vs 22% vs 8.3% for ERD and 15% vs 10% vs 3.3% for BE, respectively). Jones and coworkers already demonstrated that hiatal hernia size is the dominant determinant of esophagitis presence in GERD patients.(28)
More recently, we observed according to Bredenoord et al.(9,29) that increasing degrees of mucosa damage are associated with more severe reflux patterns in terms of all kinds of reflux (acid, weakly acid, and weakly alkaline reflux) and total AET. However, no information regarding EGJ morphology as assessed by HRM was provided in the latter two studies.
Our study shows that a disruption of EGJ is frequently correlated with a positive impedance-pH monitoring. At logistic regression, we found that Type III and Type II have a more frequent

probability to show a positive MII-pH than Type I EGJ (95% vs 84% vs 50%, respectively, $p < 0.001$). It is relevant to note that we labelled as positive those patients who had at least one abnormal parameter at 24-h monitoring, thus not only patients with an abnormal total number of refluxes or abnormal AET but also those with a positive symptom-reflux correlation. Therefore, we observed for the first time a positive correlation between EGJ morphology and symptom association analysis. This is likely due to the worsening of reflux disease associated with the increasing separation between LES and CD. Overall, these observations sustain the concept of the pathophysiological significance of perturbations of EGJ anatomy in GERD, with the recognition that EGJ morphology plays a major role as anti-reflux barrier. However, the recent findings on the mobility of the LES relative to the diaphragm in prolonged recordings, periodically converting from alignment to separation, suggest that EGJ morphology is dynamic and varies with time and activity, especially when eating.(30) These evidences suggest that EGJ function is really complex, and morphology can impact only in part on its function.

There are some limitations to mention in our study. Firstly, EGJ morphology assessment was performed only at the beginning of the manometric protocol and given the instability of EGJ, it is possible that some patients were labelled as Type I or Type II instead of a different pattern. However, the beginning of the test usually takes 5 min to make the patient more confident with the probe in their throat and this made the evaluation of the EGJ longer, as we were able to evaluate a prolonged recording. Moreover, in some cases, the catheter intubation may stimulate vomiting and increase intra-abdominal pressure, thus helping to observe EGJ changes. However, there are limited data in literature on the frequency of this potential change and it is possible that it may occur not so frequently. Secondly, HRM measures pressures from sensors located 1 cm apart and, therefore, pressure values in between are generated by taking adjacent measured pressures into account. Thus, accuracy of distances <1 cm may not be perfect. Thirdly, despite the clear and significant association between EJG morphology and GERD severity, the predictive value of EGJ morphology in terms of positivity at impedance-pH monitoring is limited, thus highlighting the absolute need to perform reflux testing to document a reflux disease.

In conclusion, the increasing separation between LES and CD, from Type I to Type III EGJ, is associated with a gradual and significant increase in reflux episodes, esophageal AET and positive reflux-symptom association. Thus, given the relatively easy feasibility of EGJ assessment during HRM and the high sensitivity and specificity of hiatal hernia detection in comparison with endoscopy and radiographic evaluation, these data emphasize the utility of performing EGJ assessment during manometry protocols and describing its morphology, in particular in patients undergoing reflux monitoring as preoperative assessment for endoscopic or surgical procedures. EGJ morphology may be useful to estimate an abnormal impedance-pH testing in patients with GERD.

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TABLE PAGES

Table 1. Demographic and clinical parameters of patients with gastroesophageal reflux disease symptoms classified on the basis of esophagogastric junction morphology

Features	Whole population	Patients with EGJ type I	Patients with EGJ type II	Patients with EGJ type III	*p*-value
Patients, *n*	130	60	50	20	
Male patients, *n* (%)	65 (50)	28 (47)	28 (56)	8 (40)	0.293
Mean age (range)	53 (21–78)	51 (25–73)	54 (35–76)	57 (21–78)	0.043
Mean BMI (range)	25 (17–33)	23 (17–28)	25 (19–33)	25 (21–30)	0.333
Alcohol consumption, *n* (%)	30 (23)	10 (17)	12 (24)	8 (40)	0.110
Coffee consumption, *n* (%)	47 (36)	20 (33)	20 (40)	7 (35)	0.537
Smoking, *n* (%)	14 (11)	6 (10)	5 (10)	3 (15)	0.460
Helicobacter pylori infection, *n* (%)	12 (9)	5 (8)	4 (8)	3 (15)	0.559
Patients having previously received PPIs, *n* (%)	118 (91)	51 (85)	47 (94)	20 (100)	0.316
Positive (>50%) symptom response, *n* (%)	65 (50)	27 (45)	23 (46)	15 (75)	0.010

Legend: EGJ, esophagogastric junction; BMI, Body Mass Index; PPIs, proton pump inhibitors.

Table 2. Incidence of abnormal esophageal acid exposure time, increased number of total reflux events and positive reflux-symptom association detected at impedance-pH monitoring among patients with different esophagogastric junction morphology.

	EGJ type I (n = 60)	EGJ type II (n = 50)	EGJ type III (n = 20)
Patients with GERD	30 (50%)	42 (84%)	19 (95%)
Patients without GERD	30 (50%)	8 (16%)	1 (5%)
Patients with abnormal TNR (>54)	6 (10%)	19 (38%)	12 (60%)
Patients with normal TNR (<54)	54 (90%)	31 (62%)	8 (40%)
Patients with abnormal AET (>4.2%)	16 (27%)	28 (56%)	15 (75%)
Patients with normal AET (<4.2%)	44 (73%)	22 (44%)	5 (25%)
Patients with positive symptom association	26 (43%)	36 (72%)	15 (75%)
Patients with negative symptom association	34 (57%)	14 (28%)	5 (25%)

Legend: EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease; TNR, total number of refluxes; AET, acid exposure time.

FIGURE PAGES

Figure 1. Esophageal AET in patients with gastroesophageal reflux disease symptoms classified on the basis of EGJ morphology. EGJ, esophagogastric junction; AET, acid exposure time.

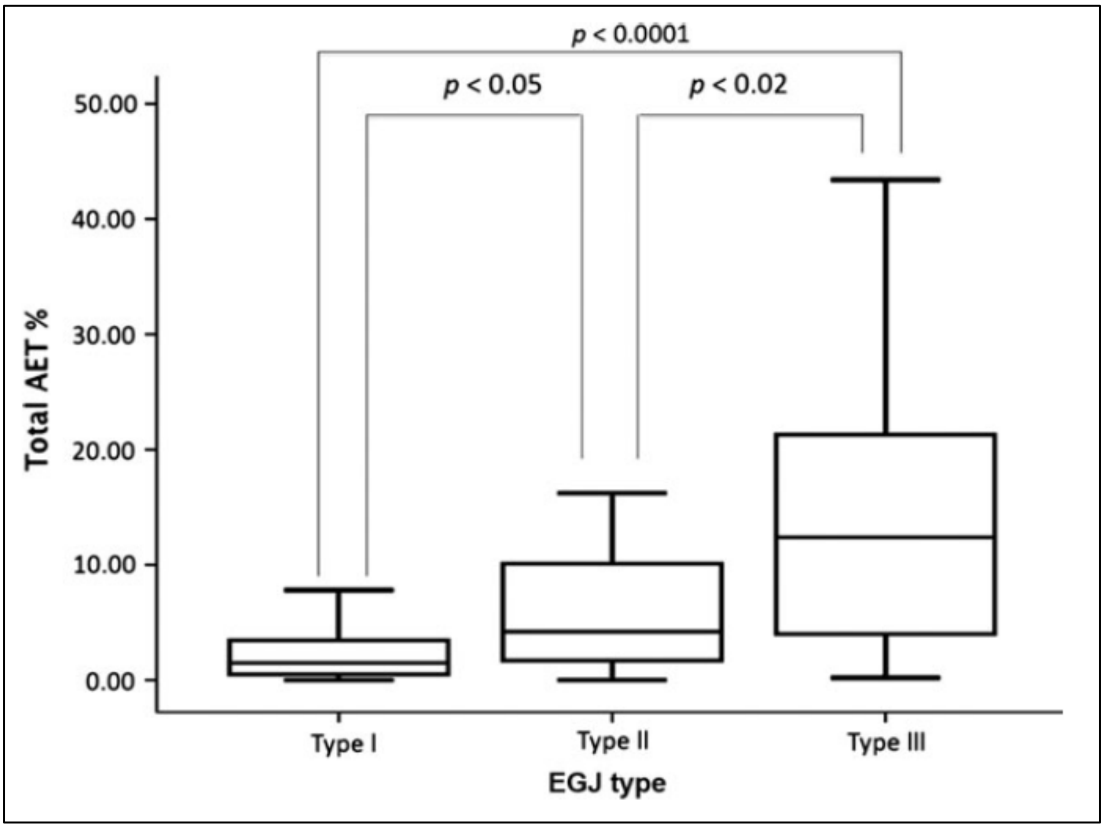

Figure 2. Number of reflux episodes in patients with gastroesophageal reflux disease symptoms classified on the basis of esophagogastric junction morphology. EGJ, esophagogastric junction; MII, multichannel intraluminal impedance.

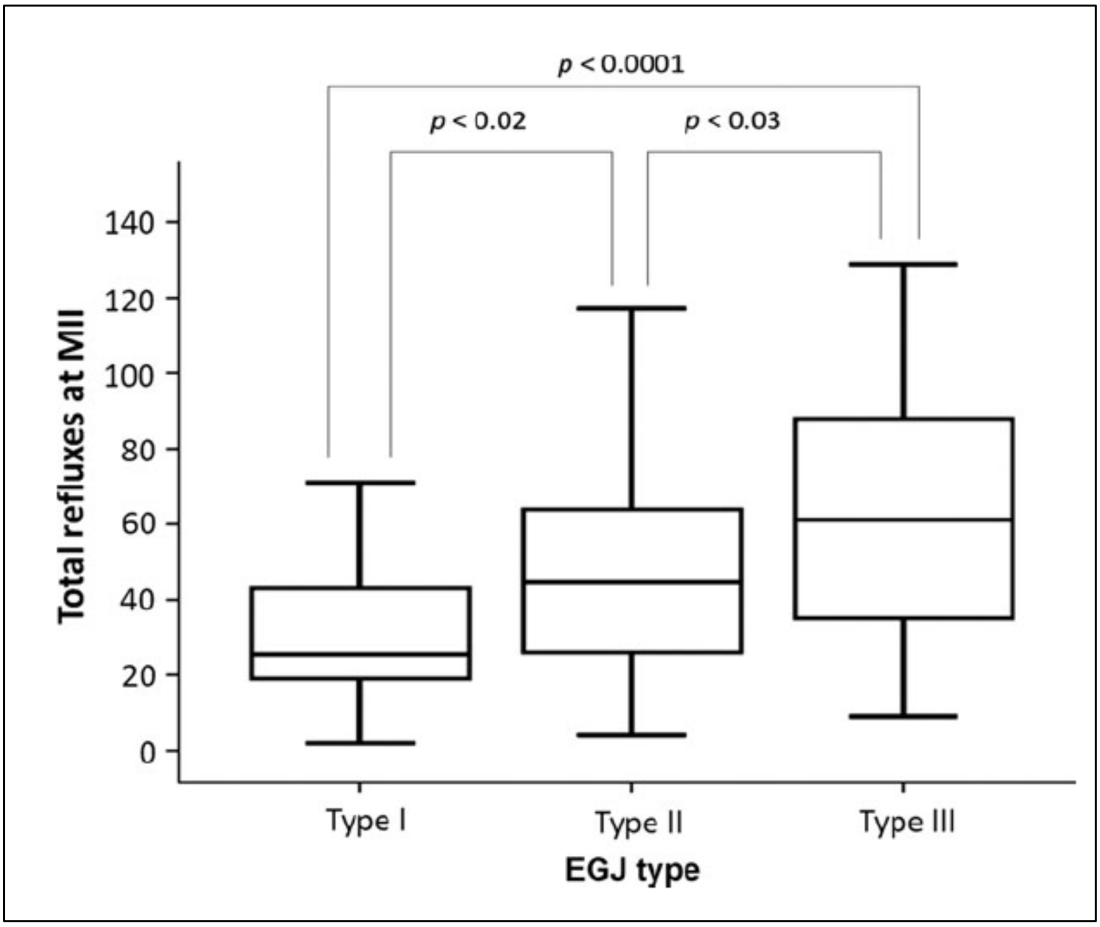

Figure 3. Reflux-symptom association in patients with gastroesophageal reflux disease symptoms classified on the basis of esophagogastric junction morphology. EGJ, esophagogastric junction.

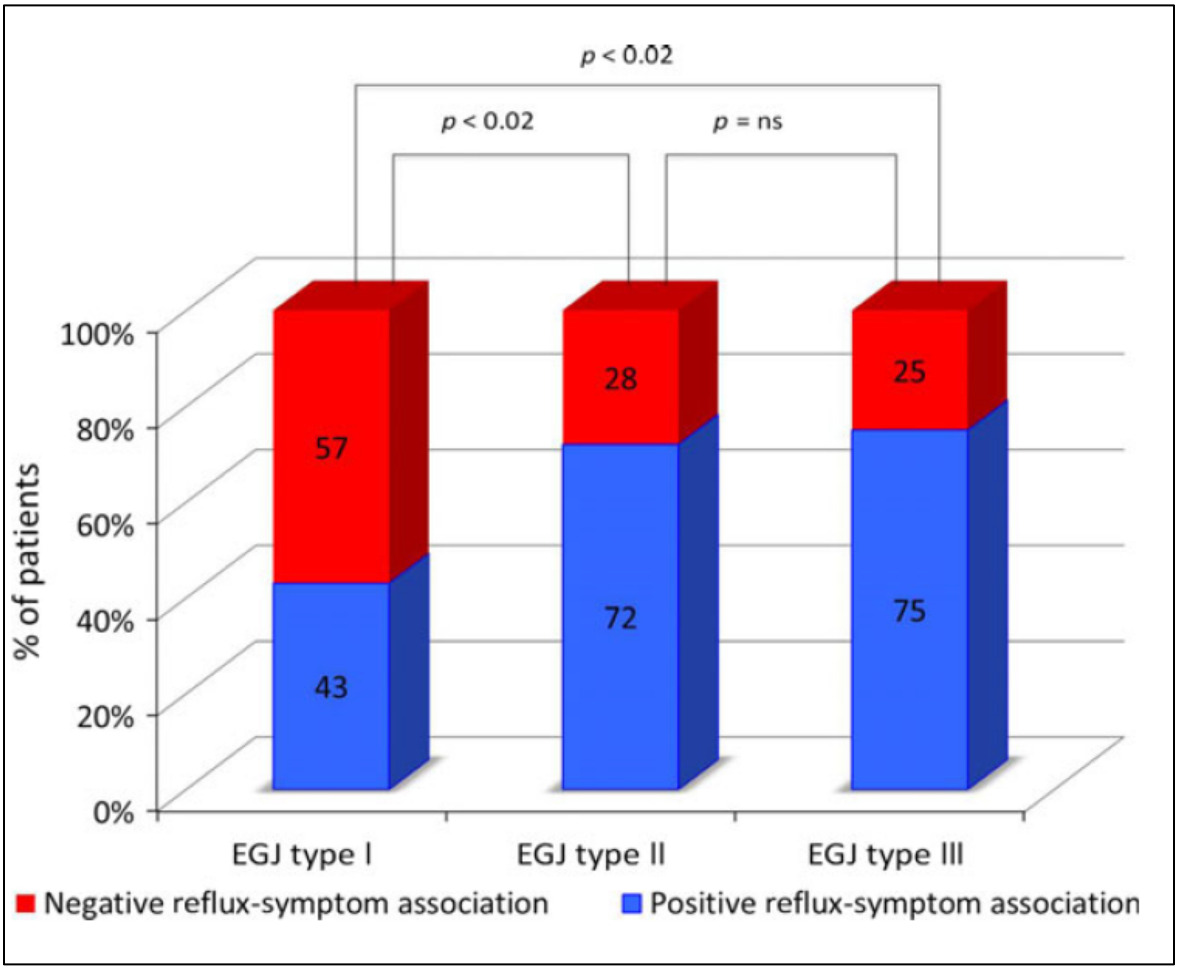

Figure 4. Normal and abnormal impedance-pH testing in patients with gastroesophageal reflux disease symptoms classified on the basis of esophagogastric junction morphololology. Abnormal impedance-pH testing was defined as the presence of abnormal acid exposure and/or abnormal number of total reflux events and/or positive reflux/symptom association. EGJ, esophagogastric junction; MII-pH, multichannel intraluminal impedance-pH monitoring.