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Is there a direct relationship between hiatal hernia size, esophageal body hypomotility and symptomatic perception of gastroesophageal reflux episodes?

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Abstract

Background The esophagogastric junction (EGJ) is classified into 3 anatomical subtypes according to lower esophageal sphincter-crural diaphragm (LES-CD) separation. We aimed to assess their relationship to esophageal motility, reflux characteristics, and symptom perception.

Methods We analyzed data from 1740 consecutive patients with typical reflux symptoms, who underwent high resolution manometry and a 24-h pH-impedance study during a 13-year period. A diagnosis of gastroesophageal reflux disease (GERD) was made if acid exposure time (AET) was >6%. EGJ types were classified as 1, 2, or 3, if LES-CD separation was up to 1 cm, 1-3 cm, or ≥3 cm, respectively.

Results EGJ type distribution was 72.2%, 22.1% and 5.7%, for types 1, 2 and 3, respectively. GERD was diagnosed in 31.2% and was more common among patients with EGJ type 2/3 vs. 1 (P<0.001). Length of LES-CD separation significantly correlated with AET and number of reflux episodes. Patients with type 2 or 3 EGJ more often showed ineffective or absent peristalsis compared with type 1 (P=0.008 and P<0.001 respectively). In the multivariate analysis, EGJ type 2/3 correlated with AET (P=0.001) and reflux episodes (P=0.041) but not with positive symptomatic markers or with ineffective/absent peristalsis.

Conclusions Our study confirms that EGJ anatomical morphology is a strong risk factor for GERD and correlates with both AET and the number of reflux events, though the length of separation is more important than the type. The multivariate analysis revealed that EGJ type 2 or 3 was not correlated with symptom perception or esophageal hypomotility.

Keywords Esophagogastric junction, gastroesophageal reflux disease, acid exposure time, esophageal symptom perception, esophageal hypomotility

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Introduction

The esophagogastric junction (EGJ) is composed of the intrinsic lower esophageal sphincter (LES) and elements of the crural diaphragm (CD), and serves as a complex anatomical and physiological antireflux barrier. The EGJ's anatomic morphology has been classified into 3 subtypes, when assessed by high-resolution manometry (HRM) [1,2]; type 1, superimposed intrinsic LES and CD; type 2, separation of LES from CD pressure signals less than 3 cm apart; and type 3, separation >3 cm [3]. Type 2 and type 3 EGJ morphology represent the clinically relevant hiatal hernia (HH) and are associated with increased esophageal acid exposure time and positive reflux–symptom association [4,5].

Type 3 EGJ morphology is associated with more severe reflux, possibly because of a lower basal LES pressure profile and lower inspiratory EGJ pressure augmentation [6,7]. There are

studies showing a relationship between HH and hypomotility in the esophageal body. Hypomotility may impair acid clearance from the esophageal lumen [4,5,8]. Previous data have also correlated HH with patients' symptoms [9]. HRM findings such as the LES-CD separation pattern, ineffective motility (IEM)/absent contractility, and hypotensive LES are considered supportive evidence for a diagnosis of gastroesophageal reflux disease (GERD) [1,3].

It is not clear whether the impact of HH on esophageal motility and symptom perception is due to the hernia itself, or is secondary to the hernia-induced gastroesophageal reflux and mucosal damage. We aimed to evaluate the EGJ characteristics in a large number of patients who underwent HRM as part of their diagnostic workup for GERD symptoms. We wanted to assess the relationship between EGJ anatomical morphology, esophageal body motility, reflux characteristics, and perception of GERD symptoms.

Patients and methods

Patients

We analyzed data from consecutive patients who underwent 24-h pH-impedance monitoring and HRM during the same visit to the upper GI Physiology Unit, Royal London Hospital. This was a retrospective analysis of tracings from patients studied between 2009 and 2022. We included patients with typical (heartburn, regurgitation) and long-lasting (≥6 months) symptoms unresponsive or partially responsive to a proton pump inhibitor (PPI). The exclusion criteria were as follows: 1) patients with solely extra-esophageal symptoms; 2) patients with a positive endoscopic GERD diagnosis, undergoing HRM/pH-impedance examinations preoperatively; 3) patients with a previous definite GERD diagnosis studied while taking PPI; 4) patients using opioids; 5) patients with history of esophageal surgery; and 6) patients with a major esophageal motility disorder (apart from absent contractility/ineffective esophageal motility, according to the Chicago IV classification) by HRM [10].

HRM and multichannel intraluminal impedance (MII) pH-monitoring protocol

Patients were instructed to stop PPI and histamine H_2 blockers for at least 7 days prior to the study. Patients underwent HRM (Medtronic, Minneapolis MN, USA) after an overnight fast. HRM studies were executed using an assembly with a 4.2-mm outer diameter and 36 solid state circumferential pressure sensors spaced at 1-cm intervals (Manoscan; Given Imaging, Los Angeles, CA, USA). Studies were performed with patients in the supine position. The manometric protocol included a 30-sec baseline recording period to assess the EGJ and at least 10 single water swallows (5 mL) at 30-sec intervals to evaluate esophageal peristalsis. Data acquisition, display and analysis were performed using dedicated software (Manoview analytical software; Given Imaging), after appropriate thermal compensation. EGJ anatomic morphology was assessed by measuring the distance between the distal margin of the LES and respiratory induced changes at the CD level. Based on these measurements, the EGJ was classified according to the Lyon Consensus into type 1, 2 or 3 depending on the separation of the crural diaphragm and the LES (type 1: no separation or separation <1 cm, type 2: 1-3 cm, type 3: ≥3 cm). LES hypotension was diagnosed if mean basal LES pressure was <13 mmHg. MII-pH monitoring was performed as follows. The MII-pH catheter (Diversatek Healthcare, Highlands Ranch CO, USA or OMOM, Jinshan Science and Technology, Chongqing, China) was placed 5 cm above the LES using a proximal pH sensor, and the distal pH sensor was placed in the stomach. The catheter has 6 impedance pairs of electrodes at 3, 5, 7, 9, 15 and 17 cm above the LES. We analyzed the MII-pH tracings using the dedicated software and by visual editing based on our standard protocol. Only pH-impedance studies in which the probe remained in place for at least 16 h were considered valid for analysis. The patients were instructed to enter into a diary to indicate the beginning and ending times of meals and changes in body position, and further to report in the same diary the exact time whenever they experienced reflux symptom, as well as the exact type of symptom. Acid exposure time (AET) was calculated as the percentage of time during which the pH was below 4 at the esophageal pH sensor.

Number of reflux episodes (NRE) and reflux-symptom association—symptom index (SI) and symptom association probability (SAP)—were documented. The SI and SAP were calculated and designated as positive for SI >50% or SAP >95%.

The GERD diagnosis was made using the Lyon consensus criteria for 24-h pH-impedance. Patents with an AET (off-PPI) >6% were considered to have GERD, 4-6% inconclusive GERD, and <4% definitely not GERD.

Since this study was a *post hoc* analysis of de-identified previously collected data from esophageal studies, with no direct link to individual patients, formal ethics approval was not deemed to be necessary.

Statistical analysis

Statistical analysis was performed using SPSS V23 (SPSS software; SPSS Inc, Chicago, IL, USA). Data were expressed as frequencies, mean ± standard deviation, or median (interquartile range), as appropriate. Normally distributed quantitative variables were compared between groups using the Student's *t*-test, and non-normally distributed variables by the Mann-Whitney test. Qualitative variables were compared using the chi-square test or Fisher's exact test, as appropriate. Since GERD diagnosis was expressed as a qualitative variable, comparisons between treatment groups were made separately (in pairs), using the chi-square test as appropriate. The associations between quantitative variables were assessed using Pearson's correlation coefficient. Multivariate logistic regression analysis models were used to identify independent

significant predictive factors of a poor dichotomous outcome. Only parameters with a significant association or a trend for a significant association (P<0.10) with the dependent variable in the univariate analysis were included in the multivariate analysis models. All tests were 2-sided and P-values <0.05 were considered to be significant.

Results

In total, 1740 patients (male/female 752 (43.2%)/988 (56.8%); mean age 51, range 16-87 years) were included in the analysis. Heartburn was reported in 1484 (85.9%) and regurgitation in 1268 (72.9%). Patients' mean body mass index was 26.8±4.8 kg/cm^2. GERD was diagnosed in 543 (31.2%) patients and excluded in 994 (57.1%). Inconclusive GERD was diagnosed in 204 (11.7%) patients. Type 1 EGJ morphology was documented in 1256 (72.2%), type 2 in 385 (22.1%), and type 3 in 99 (5.7%).

EGJ morphology and GERD diagnosis

A GERD diagnosis (AET >6%) was significantly more common among patients with EGJ type 2 (n=148, 38.4%) or type 3 (n=54, 54.4%), compared to patients with type 1 (202/484, 41.7% vs. 341/1256, 27.1%, P<0.001). Patients with type 3 EGJ were more frequently diagnosed with GERD than patients with type 2 (P<0.001). The size of LES-CD separation among patients with EGJ type 2 or 3 was larger in patients with a GERD diagnosis compared to those without (2.46±1.25 vs. 2.09±1.07 cm; P<0.001).

EGJ morphology and pH-MII findings

Patients with EGJ type 2 or 3 had a greater AET and total number of reflux episodes, and higher rates of SI and SAP positivity in comparison to patients with EGJ type 1. AET and total NRE were significantly greater among patients with type 3 EGJ, compared to patients with type 2 EGJ. This was not the case for SI or SAP positivity rate (Table 1).

In the logistic regression multivariate analysis concerning the total study group EGJ type 2 and 3 correlated with AET and the total number of reflux episodes, but not with SI or SAP positivity (Table 2).

With respect to all patients, the length of LES-CD separation significantly correlated with total AET, upright AET, supine AET, total number of reflux episodes, number of acid reflux episodes, and number of non-acid reflux episodes (Table 3).

In patients without a GERD diagnosis (AET<4%), SAP positivity did not differ among patients with EGJ type 1 vs. 2 or 3 (type 1: 292/571, 51.1% vs. type 2 or 3: 95/164, 57.9%, P=0.132) but SI positivity showed a significant difference (type 1: 208/571, 36.4% vs. type 2 or 3: 75/164, 45.7%, P=0.032).

Data concerning specific pH-metrics in patients with and without GERD and their correlation with EGJ types are given in Table 4.

GERD diagnosis and HRM findings

Patients with a GERD diagnosis (AET >6%) more frequently showed a hypotensive LES (no GERD: 565/1197, 47.2% vs. definite GERD 295/543, 54.3%, P=0.006) and IEM/absent contractility (no GERD: 441/1197, 36.8% vs. GERD: 242/543, 44.6%, P=0.003).

In the logistic regression multivariate analysis concerning the total study group, GERD diagnosis correlated with hypotensive LES (odds ratio [OR] 1.193 95% confidence interval [CI] 1.059-1.208; P=0.006), IEM/absent peristalsis (OR 1.286, 95%CI 1.038-1.592; P=0.021) and length of CD-LES separation (OR 1.314, 95%CI 1.038-1.592; P=0.001) but not with EGJ type 2 or type 3 (OR 1.007, 95%CI 0.664-1.528; P=0.973).

Table 1 Comparison of pH-impedance metrics among different EGJ types in the total cohort

pH-impedance metrics	EGJ type 1	EGJ type 2	EGJ type 3	P-value (univariate)		
				1 vs. 2	1 vs. 3	2 vs. 3
AET (%)	5.1±6.8	6.5±7.5	10.8±12.7	0.002	<0.001	<0.001
Upright AET (%)	7.5±12.1	8.6±11.1	10.5±12.5	0.310	<0.001	0.176
Supine AET (%)	5.9±13.1	6.8±13.2	10.9±17.4	0.214	<0.001	0.030
Total reflux episodes (n)	45±38	51±40	63±61	0.014	<0.001	0.023
Acid reflux (n)	25±21	31±27	37±42	<0.001	<0.001	0.091
Non-acid reflux (n)	16±19	19±22	25±33	0.002	0.031	0.098
SI positivity (%)	488/998 (51.5%)	187/298 (62.8%)	48/77 (62.3%)	0.001	0.042	>0.99
SAP positivity (%)	566/947 (59.8%)	209/298 (70.1%)	54/77 (70.1%)	0.001	0.046	>0.99

*Values are given as mean±SD

EGJ, esophagogastric junction; AET, acid exposure time; SI, symptom index; SAP, symptom association probability

EGJ morphology and other HRM findings

In the total cohort, patients with either type 2 or 3 EGJ more often showed IEM/absent peristalsis compared to patients with type 1 (44.7% and 49.5% vs. 36.9%, P=0.008 and P<0.001 respectively). The difference between type 2 vs. type 3 patients was not statistically significant (P=0.385). The larger the LES-CD separation, the weaker the esophageal body contractility. The length of LES-CD separation was negatively correlated with the mean distal contractile interval (P=0.034, R: 0.052).

In patients in whom a GERD diagnosis was definitely excluded (AET <4%) the rate of IEM/absent peristalsis did not differ among patients with EGJ type 1 vs. EGJ type 2 or 3 (type 1: 277/771, 35.9% vs. type 2 or 3: 84/223, 37.7%, P=0.636).

Data relating to IEM/absent contractility in patients with and without GERD in correlation with EGJ types are given in Table 4.

A correlation between IEM/absent peristalsis and EGJ type was found in the total study group but not among patients without GERD. To minimize the GERD-related effect on esophageal motility, we used multivariate regression binary logistic analysis (including GERD) to determine factors that were independently correlated with EGJ morphology. EGJ type 2 or 3 morphology was independently correlated with hypotensive LES (OR 0.451, 95%CI 0.361-0.564; P<0.001) and GERD diagnosis (OR 1.836, 95%CI 1.468-2.296; P<0.001), but not with IEM/absent peristalsis (OR 1.164, 95%CI 0.932-1.454; P=0.182).

Table 2 Multivariate analysis of pH-IM factors correlated with EGJ type 2/3 in the total cohort

Factors	P-value	OR	95%CI	
			Lower	Upper
AET	0.001	1.029	1.012	1.046
reflux episodes	0.041	1.003	0.999	1.007
SI	0.420	1.136	0.834	1.547
SAP	0.091	1.291	0.953	1.749

*Logistic regression multivariate analysis

pH-IM, pH-impedance monitoring, EGJ, esophagogastric junction; AET, acid exposure time; SI, symptom index; SAP, symptom association probability; CI, confidence interval

Table 3 Correlations between LES-CD separation and reflux parameters in the total cohort

Parameters	P-value	r
AET	<0.001	0.174
Upright AET	<0.001	0.128
Supine AET	<0.001	0.123
Total reflux episodes	<0.001	0.100
Acid reflux	<0.001	0.150
Non-acid reflux	<0.001	0.101

*Length of LES and CD separation and ph-Impedance metrics: Pearson correlation

LES, lower esophageal sphincter; CD, crural diaphragm; AET, acid exposure time

Discussion

It is common knowledge that an HH predisposes to GERD [11]. Our study confirms that EGJ anatomical morphology types 2 and 3 are strong risk factors for GERD development, as they correlate both with the total number of reflux events and with AET. Our study, which was based upon the largest study population examined in the literature, confirmed that EGJ type 2 and especially type 3 are associated with increased acid exposure and GERD diagnosis, as defined by the Lyon consensus [3]. Though our study shows that it is not the type of EGJ that matters most, but the length of

Table 4 Rate of ineffective esophageal motility / absent contractility and specific pH-metrics in patients with and without GERD in correlation with EGJ types

EGJ type	Ineffective esophageal motility / absent contractility (rate)	Acid exposure time (%)	Total number of refluxes	SI positivity (rate)	SAP positivity (rate)
EGJ type 1					
GERD +	134/341 (39.4%)	13.6±11.4	68±52	202/266 (75.9%)	199/265 (75.1%)
GERD -	277/771 (35.9%)	1.4±1.1	33±29	208/571 (36.4%)	292/571 (51.1%)
EGJ type 2					
GERD +	74/148 (50%)	13.4±7.2	70±50	101/123 (81.1%)	104/123 (84.6%)
GERD -	73/193 (37.8%)	1.5±1.2	36±30	63/142 (44.4%)	80/142 (56.3%)
EGJ type 3					
GERD +	33/54 (61.1%)	17.5±11.9	73±61	30/42 (71.4%)	31/42 (72.8%)
GERD -	11/30 (36.6%)	1.7±1.3	51±50	12/22 (54.5%)	15/22 (68.2%)

*Values are given as mean±SD

EGJ, esophagogastric junction; GERD, gastroesophageal reflux disease

the LES-CD separation, as underlined by our multivariate analysis.

A previous study by Ham *et al*, which included 137 symptomatic patients, detected erosive reflux disease in 15.5%, 20.8% and 24.1% of patients with EGJ type 1, 2 and 3 morphology, respectively [4]. In another study by Tolone *et al*, which included 130 symptomatic patients, abnormal impedance pH monitoring was observed in 67% of patients with type 2 or type 3 EGJ morphology. Both studies used a cutoff of >2 cm and not 3 cm for type 3 anatomical EGJ morphology, contrary to what is proposed by the Lyon consensus. Previously published data also showed that the longer the HH, the greater the risk of GERD [12]. Another study with 175 patients concluded that patients with a larger HH had more acid reflux, in both the distal and proximal esophagus, while 50% of patients with an HH >5 cm were diagnosed with Barrett's esophagus [13].

We have shown that LES-CD separation is independently correlated with low baseline LES pressure, irrespective of esophageal acid exposure, but it is not correlated with IEM/absent contractility. This observation contradicts previous studies (e.g., Schlottmann *et al*) that reported a correlation between the size of HH and the existence of esophageal motor abnormalities [9,13]. The relevant findings in previous studies arose from simple univariate analysis. However, our multivariate analysis showed that the correlation of EGJ type 2 and 3 with IEM/absent peristalsis vanishes when factors such as a diagnosis of GERD are entered into the analysis. This argument is further supported by the fact that, among patients definitely not having GERD (AET <4%), the rate of IEM/absent peristalsis did not differ among patients with EGJ type 1 vs. patients with type 2 and 3.

The relationship between HH and gastroesophageal reflux symptoms is complex. Reflux symptoms can be assessed by their severity (intensity and frequency) or by the perception of reflux events (using reflux symptom association analysis) [14,15]. We used the later in our analysis. In our univariate analysis, EGJ type 2 and 3 correlated with the patients' symptom perception, as expressed by SAP and SI positivity. However, using multivariate analysis we found that EGJ type 2 or 3 were not independently correlated with SI or SAP, but with metrics related to the severity of reflux (AET and number of reflux events). Both the abovementioned studies of Tolone and Ham correlated EGJ contractile integral and anatomical morphology of the EGJ with symptoms. Unfortunately, they only assessed this correlation by univariate analysis. As EGJ type 2 and 3 independently correlate with the presence of GERD, it is only logical that in the univariate analysis, too, they will be correlated with symptoms of GERD. Our observation, after performing multivariate analysis, suggests that reflux perception is not independently driven by anatomical alterations, but by its consequences (i.e., more acid exposure, higher reflux volume, or proximal reflux extent).

Our study was based on a retrospective analysis of motility and reflux monitoring in patients with GERD symptoms. We had no data concerning the relationship between EGJ morphology and erosive reflux disease. All patients included had persistent GERD symptoms, with no or incomplete PPI response and normal endoscopy, since this is the population for which a pH-impedance study is mainly indicated according to guidelines. EGJ contractile integral a novel metric of EGJ barrier function was not assessed in the current study. The GERD diagnosis was made on the basis of a 24-h pH-impedance study; therefore, the day-to-day variability of esophageal acid exposure could not be taken into consideration. Moreover, no analysis was specifically performed for patients with inconclusive GERD (AET 4-6%) which comprised 11.7% of our cohort. GERD diagnosis in such patients is driven by supportive evidence. Unfortunately, supportive evidence, such as mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave, were not available in our cohort.

Summarizing, our study confirms that EGJ anatomical morphology type 2 and 3 are strong risk factors for GERD and correlate with both acid exposure and the number of reflux episodes. The longer the length of LES-CD separation, the stronger the correlation. However, our multivariate analysis showed that the relationship between the size of an HH on the one hand, and esophageal hypomotility and reflux symptom perception on the other, is mainly driven by the resultant acid reflux and is not an independent effect of the hernia. Therefore, in the absence of GERD, esophageal symptoms and dysmotility cannot be attributed to the existence of an HH. As a consequence, surgical correction of the HH will most probably not lead to their resolution. Therefore, it is crucial to underline the importance of the pre-surgical 24-h pH-impedance study among patients referred for esophageal HRM preoperatively before HH surgical correction, since GERD (but not HH) is usually the main cause of esophageal hypomotility and of their symptoms. Nonetheless, HH is a strong risk factor for GERD development and it must be underlined that day-to-day variability of esophageal acid exposure should be taken seriously into consideration when evaluating pH-impedance studies, before refuting a GERD diagnosis [16,17]. This is especially so in patients who show more than one kind of evidence in support of a GERD diagnosis (i.e., HH, esophageal dysmotility, LES hypotension, low MNBI, etc.) [3].

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Summary Box

What is already known:

- According to the Lyon Consensus, the anatomic morphology of the esophagogastric junction (EGJ) has been classified into 3 subtypes based on high-resolution manometry (HRM): type 1, superimposed intrinsic lower esophageal sphincter (LES) and crural diaphragm (CD); type 2, separation of LES to CD pressure signals less than 3 cm; and type 3, separation >3 cm
- Types 2 and 3 EGJ morphology represent the types clinically relevant to hiatal hernia (HH) and are associated with greater esophageal acid exposure time and positive reflux-symptom association
- Previous data have correlated HH with esophageal dysmotility and symptoms

What the new findings are:

- EGJ anatomical morphology type 2 or 3 was a strong risk factor for gastroesophageal reflux disease (GERD) and correlated with both acid exposure and the number of reflux episodes; the longer the length of LES-CD separation, the stronger the correlation
- Esophageal hypomotility and reflux symptom perception are mainly driven by the resultant acid reflux and not by the HH itself
- In the absence of a documented diagnosis of reflux disease, HH repair will most probably not lead to resolution of symptoms

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