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Correlation between symptoms and reflux in patients with gastroesophageal reflux disease

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ABSTRACT – Background – Esophageal symptoms of gastroesophageal reflux are the same in functional heartburn, non-erosive disease, and erosive disease. Their patient-perceived intensity may be related to gastroesophageal reflux intensity. **Objective** – To evaluate whether the symptoms in GERD patients are related to the intensity of gastroesophageal acid reflux. **Methods** – To test this hypothesis, 68 patients with heartburn (18 with functional heartburn, 28 with non-erosive reflux disease, and 22 with erosive reflux disease) had their symptoms evaluated by the Velanovich score (which mainly focuses on heartburn) and the Eating Assessment Tool (EAT-10) (which focuses on dysphagia). They were submitted to esophageal endoscopy and then, on another day, they answered the Velanovich and EAT-10 questionnaires and underwent manometry and 24-hour pHmetry (measured 5 cm proximal to the upper border of the lower esophageal sphincter). **Results** – The Velanovich score was higher in patients with non-erosive and erosive diseases than in those with functional heartburn. The mean EAT-10 score did not differ between functional heartburn, erosive, and non-erosive gastroesophageal reflux disease. Considering the threshold of ≥5 to define dysphagia, 4 (22%) patients with functional heartburn, 12 (43%) with non-erosive disease, and 9 (41%) with erosive disease had dysphagia (P=0.18). There was: a) a moderate correlation between the Velanovich and DeMeester score and between Velanovich score and the percentage of acid exposure time (AET); b) a weak correlation between EAT-10 and DeMeester score and between EAT-10 and acid exposure time. **Conclusion –** There is a moderate positive correlation between heartburn and gastroesophageal reflux measurement. Dysphagia has a weak positive correlation with reflux measurement.

Keywords – Esophagus; gastroesophageal reflux; heartburn; esophagitis; deglutition disorders.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is highly prevalent in the world population[1-3]. Heartburn and acid regurgitation are the most frequent symptoms, although the disease also causes chest pain, dysphagia, globus sensation, belching, chronic cough, and hoarseness[3]. It results from the return of acid secretion and other gastric juice components from the stomach to the esophagus, causing troublesome symptoms, mucosal lesions, and complications[2,4-6].

The amount of refluxate and/or the duration of reflux in GERD may cause more intense and/or longer symptoms in a given population[5]. The symptoms are influenced by cultural and personal factors[6-8], leading to different manifestations in patients from different countries and communities.

The manifestations in GERD patients represent distinct phenotypes[4,9]. They may have symptoms when esophageal acid exposure is normal or abnormal, and with or without mucosa lesions[4]. The exposure of esophageal mucosa to lower pH (below four) causes more frequent symptoms[10], although they can also occur when the esophageal pH is between four and seven[11].

The objective of this investigation was to evaluate whether the symptoms in GERD patients are related to the intensity of gastroesophageal acid reflux. The hypothesis was that the more intense the gastroesophageal reflux, the more intense the symptoms.

METHODS

The sample comprised 68 consecutive patients, aged 17 to 79 years, who came to the outpatient clinic between 2017 and 2019 to investigate the cause of heartburn. They were evaluated with endoscopy, 24-hour esophageal pH monitoring, the Velanovich scale[12,13], and the Eating Assessment Tool (EAT-10)[14,15]. The inclusion criteria were patients with heartburn at least three times a week for more than one year who agreed to participate in the research. The exclusion criteria were patients with obesity, pulmonary diseases, esophageal achalasia, immunological diseases, eosinophilic esophagitis, neoplastic lesions of the esophagus, Barrett esophagus, weight loss in the previous month, chronic intake of anti-inflammatory drugs, and who did not agree to participate. To avoid bias in the information given in the questionnaires, patients who could not read and understand the questions were not included.

The investigation was approved by the Human Research Ethics Committee of the Ribeirão Preto Public University Hospital, IRB number 12220/2016. Written informed consent was obtained from each participant, whose anonymity was ensured.

The Velanovich scale, which focuses mainly on heartburn, has 10 questions, each of them with a score ranging from 0 to 5 (0 for absent symptoms and 5 for incapacitating symptoms); the maximum total score is 50. The EAT-10, which evaluates the patient for

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dysphagia, also has 10 questions each of them with a score ranging from 0 to 4 (0 for the absence of problems and 4 for the presence of severe problems); the maximum total score is 40. The method evaluates dysphagia based on patient-perceived difficulty swallowing.

The patients were first submitted to endoscopy and then, on another day, they answered the Velanovich and EAT-10 questionnaires, and underwent esophageal manometry and pHmetry. The esophageal manometry was performed with the conventional water perfusion method (Alacer, São Paulo, Brazil) to localize the upper border of the lower esophageal sphincter (LES). Each patients made 10 water swallows in the supine position, with measurement of the LES pressure and contractions at 5 cm, 10 cm and 15 cm from LES. The pH sensor (Alacer, São Paulo, Brazil) was placed 5 cm away from the upper border of the LES and recorded the intraesophageal pH for 24 hours. The examination took place after interrupting for 1 week the treatment with proton pump inhibitor and/or H_2 receptor blockers and for 24 hours the treatment with antacids or alginates.

Endoscopy and pHmetry results classify the patients into three groups: a) functional heartburn (FH) – patients with no erosive lesions in the esophageal mucosa, normal results in the 24-hour esophageal pH monitoring, and negative reflux-symptom association; b) non-erosive reflux disease (NERD) – patients with non-erosive lesions in the esophageal mucosa but with abnormal results in the 24-hour esophageal pH monitoring; c) erosive reflux disease (ERD) – patients with erosive lesions in the esophageal mucosa and abnormal results in the 24-hour esophageal pH monitoring[16,17]. Erosive reflux disease was classified following the Los Angeles classification[18]. There was no patient with reflux hypersensitivity, patients who have physiological reflux and a positive symptom association[5].

The intensity of the gastroesophageal acid reflux was quantified with the DeMeester score[19,20] and the percentage of the time the esophageal pH was below four (named acid exposure time – AET)[1]. The DeMeester score was calculated with the pH evaluation program, considering the total number of reflux episodes, the number of reflux episodes longer than 5 minutes, the total percentage of the time the pH was below four (AET), the percentage of the time the pH was below four in the upright position, the percentage of the time the pH was below four in the supine position, and the longest reflux episode[20]. We set the DeMeester threshold score of increase in esophageal acid exposure at 14.7[20]; in acid exposure time (AET), at 4%[1,21]; and for dysphagia, at five[22].

Statistical analysis

We presented the results as mean, standard deviation, median, and correlation coefficient, and conducted the statistical analysis with the regression quantiles[23], Spearman's correlation coefficient (rho), and the log-binomial regression model[24]. The differences in results and correlations were considered significant when $P \leq 0.05$. The Spearman's correlation coefficient (rho) was classified as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79) and very strong (0.80–1.00).

RESULTS

Eighteen patients were diagnosed with FH – 14 (78%) women and 4 (22%) men (aged 27 to 79 years); 28, with NERD – 17 (61%) women and 11 (39%) men (aged 21 to 79 years); and 22, with ERD – 9 (41%) women and 13 (59%) men (aged 17 to 63 years). Ten patients were graded A in the Los Angeles classification of erosive esophagitis; eight were graded B; three were graded C; and one was graded D. Ineffective esophageal motility was observed in 6 (9%) of the patients.

There was no difference in age, weight, height, and BMI between the groups (TABLE 1). The Velanovich score was lower in patients with FH than in patients with NERD and ERD ($P<0.01$, TABLE 1). There was a trend toward a significant difference between NERD and ERD (higher in ERD) in the Velanovich and DeMeester scores ($P=0.06$). There was no difference in the mean EAT-10 score between FH, NERD, and ERD. The threshold for dysphagia in EAT-10 was ≥5, which revealed the symptom in 4 (22%) patients with FH; in 12 (43%) with NERD; and in 9 (41%) with ERD, with no significant differences ($P>0.18$).

There was a correlation between the symptoms and gastroesophageal reflux quantification ($P<0.01$). However, the correlation was weak between EAT-10 and DeMeester score (rho=0.33) and between EAT-10 and AET (rho=0.30). The Velanovich score moderately correlated with the DeMeester score (rho=0.44) and with AET (rho=0.41). EAT-10 strongly correlated with the Velanovich score (rho=0.75), while the DeMeester score correlated very strongly with AET (rho=0.98) (TABLE 2).

Patients with ineffective esophageal motility (n=6) did not have higher EAT-10 scores than patients with normal esophageal motility.

There was no correlation between BMI and the Velanovich score, EAT-10 score, DeMeester score, and AET ($P>0.30$).

DISCUSSION

The results showed a moderate correlation between the GERD symptoms (evaluated with the Velanovich method) and the reflux intensity (evaluated with the DeMeester score and AET).

Symptoms are present in different GERD phenotypes, both erosive and non-erosive, and in FH[9,16]. FH is not reflux-mediated and is caused by an increase in the global sensitivity to different stimuli[25]. In this disease, there is no impairment of chemical clearance, which in turn is more intense in ERD than in NERD[26]. In FH, the Velanovich score is lower than in NERD and ERD, suggesting that heartburn can be influenced by the disease presentation of the gastroesophageal reflux spectrum. The DeMeester score and AET were lower in patients with FH. Nevertheless, the diagnosis criteria establish that these patients should have normal results, lower ones than in NERD and ERD.

Heartburn, measured with the Velanovich score, is strongly correlated with EAT-10, suggesting that dysphagia is related to heartburn and global symptoms. Higher Velanovich scores (i.e., more intense symptoms) were associated with higher acid reflux evaluation. The frequency of symptoms is associated with the pH monitoring diagnosis of GERD[27].

The modulation of heartburn is the noxious stimulation of nociceptive receptors expressed in afferent nerves[28]. The transient receptor potential cation channel subfamily V member 1 (TRPV1) plays a role in the perception of esophageal acid reflux symptoms, not correlated with acid exposure[29]. In this investigation, acid exposure was moderately correlated with symptoms evaluated with the Velanovich score. NERD patients have more superficial afferent nerves in proximal and distal esophagus than controls or ERD patients[30], and have an increased expression of TPRV1 on superficial sensory nerves than ERD patients[31]. Deep intrapapillary

TABLE 1. Evaluation results of patients with functional heartburn (FH, n=18), non-erosive reflux disease (NERD, n=28), and erosive reflux disease (ERD, n=22).

	FH		NERD		ERD	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Age (years)	47.9 (15.5)	49.0	47.3 (14.8)	47.5	39.0 (12.2)	38.0
Weight (kg)	71.7 (19.5)	73.3	78.2 (14.6)	76.2	80.8 (15.8)	79.5
Height (cm)	163.9 (10.4)	165.0	168.4 (11.7)	166.5	168.8 (9.9)	169.0
BMI (kg/m²)	26.7 (6.2)	27.4	27.5 (4.0)	26.4	28.6 (5.7)	28.5
EAT-10 score	6.8 (8.3)	4.0	9.9 (11.7)	4.0	7.4 (9.1)	4.0
Velanovich score	19.3 (14.9)*	20.5	25.9 (15.0)⁺	27.5	28.2 (13.5)	32.0
DeMeester score	8.1 (3.8)	6.7	38.9 (27.5)⁺	31.0	58.5 (43.0)	44.5
AET (%)	1.3 (1.1)	1.0	7.0 (5.8)	5.6	10.9 (8.4)	8.4

NERD: non-erosive reflux disease; ERD: erosive reflux disease; FH: functional heartburn; BMI: body mass index; SD: standard deviation; AET: acid exposure time; EAT: Eating Assessment Tool. *P< 0.01 vs NERD and ERD; ⁺P=0.06 vs ERD.

TABLE 2. Spearman's correlation coefficient (rho) between symptom scores and gastroesophageal reflux intensity.

Correlation	rho	*P*
EAT-10 – DeMeester score	0.33	<0.01
EAT-10 – AET	0.30	<0.01
Velanovich – DeMeester score	0.44	<0.01
Velanovich – AET	0.41	<0.01
EAT-10 – Velanovich	0.75	<0.01
DeMeester score – AET	0.98	<0.01

AET: acid exposure time; EAT: Eating Assessment Tool.

nerve endings did not express TRPV1 in patients with FH, NERD, or ERD[31]. Patients with FH have mucosa innervation closer to that of healthy asymptomatic subjects[32], a possible explanation for less intense symptoms.

Non-obstructive dysphagia is a frequent symptom in GERD patients, reported in 37.0%[33], 46.8%[34], 28.0%[35], and 48.3%[22] of them, depending on the method of evaluation and definition of dysphagia. Dysphagia is more frequent in patients with severe (43%) than mild esophagitis (35%)[33]. Similar to the results of this investigation, previous ones described that acid reflux patterns are unrelated to dysphagia[34]. Dysphagia frequency in this paper was higher than expected because of the evaluation method, which may have detected mild dysphagia not spontaneously reported by the patients. Cultural diversity has a significant influence on the expression of troublesome symptoms[7,8]. Dysphagia in GERD may be caused by upper esophageal sphincter dysfunction[36], esophageal hypersensitivity, and/or esophageal dysmotility[22]. Dysphagia is correlated with the overall gastroesophageal reflux symptoms – particularly heartburn, whose treatment decreases dysphagia frequency[33,37], reinforcing the association between them.

Dysphagia could be associated with ineffective esophageal motility[37], which was not seen in this investigation, however, the number of patients with esophageal motility alteration was small, not sufficient to draw conclusions.

This investigation has limitations. The EAT-10 method may not be the best way to evaluate dysphagia – although it is frequently used with this objective, it has been translated into a significant number of languages[22] (thus investigating the prevalence of dysphagia in multiple nationalities)[38], and is also used to evaluate airway aspiration[39]. Likewise, the Velanovich score may not be the perfect symptom evaluation method. Cultural aspects and limitations and individual behavior influences symptom perception and manifestations[7,8]. Therefore, no method perfectly fulfills this purpose in all populations, even within the same country.

Patients who could not understand and answer the questions of the evaluation instruments were not included in this investigation. Result generalizability may be limited because symptom manifestations are significantly influenced by people's culture, education, religion, traditions, history, dietary preference, and other issues[7,8].

In conclusion, heartburn are moderately correlated with gastroesophageal reflux intensity, whereas dysphagia has a weak correlation with the reflux intensity.

Authors' contribution

Batista AO and Dantas RO: participated in study conceptualization, data collection, results discussion, manuscript preparation, and the decision to submit the manuscript for publication.

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Batista AO, Dantas RO. Correlação entre sintomas e refluxo em pacientes com doença do refluxo gastroesofágico. Arq Gastroenterol. 2022;59(2):184-7.

RESUMO – Contexto – Os sintomas esofágicos do refluxo gastroesofágico são os mesmos na pirose funcional, doença do refluxo não erosiva e doença erosiva. A intensidade percebida pelo paciente pode estar relacionada à intensidade do refluxo gastroesofágico. **Objetivo** – Avaliar se os sintomas em pacientes com doença do refluxo gastroesofágico estão relacionados à intensidade do refluxo. **Métodos** – Sessenta e oito pacientes com pirose (18 com pirose funcional, 28 com doença do refluxo não erosiva e 22 com doença erosiva) tiveram seus sintomas avaliados pelo escore de Velanovich (que avalia principalmente pirose) e o Instrumento de Autoavaliação da Alimentação (EAT-10) (que avalia disfagia). Os pacientes foram submetidos à endoscopia esofágica e, em outro dia, responderam aos questionários Velanovich e EAT-10 e realizaram manometria e pHmetria de 24 horas (medida 5 cm proximal à borda superior do esfíncter esofágico inferior). **Resultados** – O escore de Velanovich foi maior em pacientes com doença não erosiva e doença erosiva do que naqueles com pirose funcional. A pontuação média da EAT-10 não diferiu entre pirose funcional, doença do refluxo gastroesofágico erosiva e não erosiva. Considerando o limiar ≥5 para definir disfagia, 4 (22%) pacientes com pirose funcional, 12 (43%) com doença não erosiva e 9 (41%) com doença erosiva apresentavam disfagia (*P*=0,18). Houve: a) correlação moderada entre os escores de Velanovich e DeMeester e entre os escores de Velanovich e o percentual de tempo de exposição ao ácido (AET); b) uma correlação fraca entre o EAT-10 e o escore DeMeester e entre o EAT-10 e o tempo de exposição ao ácido. **Conclusão** – Existe uma correlação positiva moderada entre a pirose e a medida do refluxo gastroesofágico. Disfagia tem correlação fraca com a medição do refluxo.

Palavras-chave – Esôfago; refluxo gastroesofágico; pirose; esofagite;transtornos de deglutição.

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