

Gastroesophageal and extraesophageal symptoms in patients with gastroesophageal reflux disease: An endoscopy-based study in Albania

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Abstract

Aim: To compare the prevalence and severity of gastroesophageal and extraesophageal symptoms in patients with gastroesophageal reflux disease (GERD) in Albania.

Methods: In this descriptive study, we investigated 248 patients (mean age: 46.5±16.3 years) diagnosed with erosive esophagitis by upper endoscopy. We assessed the severity of esophagitis by Los Angeles (LA) classification and the gastroesophageal and extraesophageal symptoms by a standard questionnaire. The prevalence of symptoms between mild erosive esophagitis (LA grade A/B: 230 patients) and severe erosive esophagitis (LA grade C/D: 18 patients) were described and reported.

Results: The prevalence of severe gastroesophageal symptoms (heartburn, acid regurgitation, and dysphagia) was higher in patients with severe erosive esophagitis than in those with mild erosive esophagitis. Patients with severe erosive esophagitis also had a higher prevalence of extraesophageal symptoms (cough and sore throat) than patients with mild erosive esophagitis (44% vs. 19% and 28% vs. 16%, respectively).

Conclusions: The prevalence of gastroesophageal and extraesophageal symptoms were higher among patients with severe erosive esophagitis. In the future, prospective clinical studies in multiple medical centers are warranted to generalize our findings in the overall Albanian population.

Keywords: erosive esophagitis, extraesophageal symptoms, gastroesophageal reflux disease.

Introduction

Gastroesophageal reflux (GR) consists in the reflux of gastric contents into the esophageal lumen, causing a large clinical spectrum of symptoms resulting in gastroesophageal reflux disease (GERD). The reflux of gastric acid juice into the esophagus may interest not only the esophageal mucosa, but may also damage the upper aerodigestive tract, including the mouth, throat, bronchi and lungs.

Although it is well-known that heartburn, acid regurgitation, nausea and epigastric pain are the typical esophageal manifestations of GERD (1), extraesophageal symptoms such as throat cleaning, coughing, sore throat and wheezing are now acknowledged as parts of the disease spectrum (2,3). On the other hand, a part of the patients with GERD are asymptomatic, particularly the older ones (4). Currently, a worldwide consensus accepts that the presence of reflux symptoms or reflux esophagitis alone is sufficient for the diagnosis of GERD (1).

In most cases, there is evidence that the severity of symptoms does not completely correlate with severity of mucosal damage (5), whereas the amount of esophageal acid exposure seems to be related to the frequency of symptoms (6,7). Also, a systematic review reported that the accuracy of heartburn or acid regurgitation in diagnosing GERD had a relatively poor sensitivity [a pooled sensitivity of 55% (95% CI=45%-68%)] (8). Thus, these results showed that the presence or absence of esophagitis may not be predicted only by the profile of symptoms. Furthermore, there are sufficient data on the clinical characteristics of GERD in patients with laryngeal or respiratory symptoms (3,9,10), but little is known about the prevalence of extraesophageal symptoms in the patients with GERD esophagitis.

The objective of our study was to compare the prevalence and severity of gastroesophageal and extraesophageal symptoms in a group of Albanian patients with GERD diagnosed by endoscopy.

Methods

Study population and patient selection

This was a cross-sectional study conducted at the Regional Hospital of Durres, the main district in central Albania, from January 2013 to June 2014. The study recruited consecutive patients aged 18-70 years who presented with typical and/or atypical reflux symptoms and who were referred or came directly to our Endoscopy Unit where they were diagnosed with reflux esophagitis by upper gastrointestinal endoscopy. The reflux esophagitis was graded according to the Los Angeles (LA) classification criteria based on the extent of visible erosions (11): grade A, one or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds; grade B, one or more mucosal breaks more than 5 mm long, none of which extends between the tops of the mucosal folds; grade C, mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference; and grade D, mucosal breaks which involve at least 75% of the esophageal circumference. Patients were further divided into two groups according to the severity of esophagitis: LA grade A/B: mild erosive esophagitis, and severe erosive esophagitis: LA grade C/D. Hiatus hernia was recorded as the occurrence of the Z line more than 2 cm above the cardio-oesophageal junction. Exclusion criteria were: (i) previous GERD; (ii) Barrett's esophagus; (iii) history of gastrointestinal surgery and/or gastrointestinal malignancies; (iv) taking any acid-suppressive drugs within the last four weeks before endoscopy; (v) use anticholinergics or prokinetics drugs; (vi) pregnancy, and; (vii) severe diseases of other organs.

We assessed the socio-demographic data, medical history and symptoms from each patient at the time of endoscopy. The socio-demographic data included age, sex, place of residence, marital status, educational level, employment status and income level. The gastroesophageal symptoms of GERD

are defined as presence of heartburn, acid regurgitation, epigastric pain, nausea, vomiting and dysphagia. Heartburn is defined as a retrosternal burning sensation (1). Acid regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or throat (1). Epigastric pain is defined as burning or gnawing epigastrium pain. Dysphagia is defined as impairment of the passage of solid/liquid foods from the mouth into the stomach (1). Patients were also asked to self-assessment individually severity of their symptoms which were divided into two categories: mild-moderate or severe. We defined the extra-esophageal symptoms of GERD as throat cleaning, chronic cough and sore throat. Chronic cough was defined as a cough that persists eight weeks or longer without having lung disorders. Throat clearing was defined as an instinctive attempt to remove an irritant in the throat. Sore throat was defined as a pain, scratchiness or irritation of the throat that often worsens when swallows without

bacterial or viral infection.

Regarding the statistical analysis, the prevalence of symptoms between mild erosive esophagitis (LA grade A/B: 230 patients) and severe erosive esophagitis (LA grade C/D: 18 patients) were described and reported.

Results

Table 1 presents the baseline characteristics of patients with GERD included in this study (N=248). The overall mean age in the study sample was 46.5 ± 16.3 years. About 66% of the patients were residing in urban areas compared with 34% who were rural residents. About 72% of participants were currently married. About 36% of the patients had a low educational level, whereas 19% had a high educational attainment. About 36% of male and female participants were currently unemployed. Finally, 58% of the patients with GERD reported a low income level (Table 1).

Table 1. Demographic and socioeconomic characteristics in a sample of patients with GERD in Albania in 2013-2014

Variable	Men (N=142)	Women (N=106)	Total (N=248)
Age (years)	$46.6 \pm 16.3^*$	46.3 ± 16.4	46.5 ± 16.3
Place of residence:			
Urban areas	93 (65.5) [†]	70 (66.0)	163 (65.7)
Rural areas	49 (34.5)	36 (34.0)	85 (34.3)
Marital status:			
Single/divorced/widowed	40 (28.2)	30 (28.3)	70 (28.2)
Married	102 (71.8)	76 (71.7)	178 (71.8)
Educational level:			
Low	50 (35.2)	39 (36.8)	89 (35.9)
Middle	72 (50.7)	39 (36.8)	111 (44.8)
High	20 (14.1)	28 (26.4)	48 (19.4)
Employment status:			
Employed/pension	88 (62.0)	71 (67.0)	159 (64.1)
Unemployed	54 (38.0)	35 (33.0)	89 (35.9)
Income level:			
Low	82 (57.7)	61 (57.5)	143 (57.7)
Average-high	60 (42.3)	45 (42.5)	105 (42.3)

* Mean values \pm standard deviations.

[†] Numbers and column percentages (in parentheses).

Table 2 presents the degree of severity of gastroesophageal symptoms in patients with mild GERD (grades A and B) and severe GERD (grades C and D). The degree of severe heartburn was higher in patients with severe GERD compared with the patients with mild GERD (72% vs. 51%, respectively). The prevalence of severe regurgitation was slightly higher in patients with severe GERD than in those with mild GERD (78% vs. 70%, respectively).

On the other hand, the prevalence of severe epigastric pain was remarkably higher in patients with severe GERD compared with their counterparts with mild GERD (83% vs. 42%, respectively). Conversely, the prevalence of severe nausea was somehow comparable between the two groups (67% vs. 60%, respectively). Finally, severe dysphagia was significantly more prevalent among patients with severe GERD than in those with mild GERD (39% vs. 20%, respectively) (Table 2).

Table 2. Distribution of gastroesophageal symptoms in patients with mild and severe GERD

Variable	Mild GERD (grade A/B) [N=230]	Severe GERD (grade C/D) [N=18]	Total [N=248]
Heartburn:			
Mild-moderate	113 (49.1)*	5 (27.8)	118 (47.6)
Severe	117 (50.9)	13 (72.2)	130 (52.4)
Regurgitation:			
Mild-moderate	68 (29.6)	4 (22.2)	72 (29.0)
Severe	162 (70.4)	14 (77.8)	176 (71.0)
Epigastric pain:			
Mild-moderate	134 (58.3)	3 (16.7)	137 (55.2)
Severe	96 (41.7)	15 (83.3)	111 (44.8)
Nausea:			
Mild-moderate	91 (39.6)	6 (33.3)	97 (39.1)
Severe	139 (60.4)	12 (66.7)	151 (60.9)
Dysphagia:			
Mild-moderate	183 (79.6)	11 (61.1)	194 (78.2)
Severe	47 (20.4)	7 (38.9)	54 (21.8)

* Numbers and column percentages (in parentheses).

Table 3 presents the prevalence of other disorders among male and female patients with GERD. The prevalence of gastric ulcer was significantly higher in male patients compared with their female counterparts (17% vs. 7%, respectively). Similarly,

the prevalence of hiatal hernia was higher in men compared with women (25% vs. 14%, respectively). On the other hand, the prevalence of gastritis was higher in women compared with men (49% vs. 39%, respectively).

Table 3. Prevalence of other disorders in patients with GERD by sex

Variable	Men (N=142)	Women (N=106)	Total (N=248)
Gastric ulcer:			
No	118 (83.1)*	99 (93.4)	217 (87.5)
Yes	24 (16.9)	7 (6.6)	31 (12.5)
Hiatus hernia:			
No	106 (74.6)	91 (85.8)	197 (79.4)
Yes	36 (25.4)	15 (14.2)	51 (20.6)
Gastritis:			
No	87 (61.3)	54 (50.9)	141 (56.9)
Yes	55 (38.7)	52 (49.1)	107 (43.1)

* Numbers and column percentages (in parentheses).

Table 4 presents the prevalence of extra-gastroesophageal symptoms in patients with mild GERD (grades A and B) and severe GERD (grades C and D). The prevalence of throat clearing was comparable between the two groups (33% in patients with severe GERD vs. 29% in those with mild GERD). On the other hand, the

prevalence of chronic cough was considerably higher in patients with severe GERD compared with their counterparts who had mild GERD (44% vs. 19%, respectively). Likewise, the prevalence of sore throat was higher among patients with severe GERD than in patients with mild GERD (28% vs. 16%, respectively) (Table 4).

Table 4. Distribution of extragastroesophageal symptoms in patients with mild and severe GERD

Variable	Mild GERD (grade A/B) [N=230]	Severe GERD (grade C/D) [N=18]	Total (N=248)
Throat clearing:			
No	163 (70.9)*	12 (66.7)	175 (70.6)
Yes	67 (29.1)	6 (33.3)	73 (29.4)
Chronic cough:			
No	186 (80.9)	10 (55.6)	196 (79.0)
Yes	44 (19.1)	8 (44.4)	52 (21.0)
Sore throat:			
No	193 (83.9)	13 (72.2)	206 (83.1)
Yes	37 (16.1)	5 (27.8)	42 (16.9)

* Numbers and column percentages (in parentheses).

Discussion

The present study is the first investigation on the frequency of gastroesophageal and extraesophageal symptoms among different categories of GERD-related esophagitis, as well as the severity of symptoms in patients with erosive esophagitis in Albania. We found that the prevalence of severe gastroesophageal symptoms (heartburn, regur-

gitation, and dysphagia) and extraesophageal symptoms (cough and sore throat) were higher in patients with severe GERD (grade C/D) than in those with mild GERD (grade A/B). We also demonstrated that, in the majority of the Albanian GERD patients, the severe typical GERD clinical symptoms prevailed.

Our findings are similar to previous studies reporting that the amount of esophageal acid exposure might be related with the frequency and severity of symptoms (6,7). Examining the characteristics of reflux episodes in patients with different degrees of esophagitis, Bredenoord et al. showed that the number of all reflux and weekly acidic reflux episodes is increased in patients with severe oesophagitis (12), whereas in a case control-study, Savarino et al. reported a higher proportion of reflux episodes reaching the proximal esophagus in patients with erosive esophagitis, compared with a control group (13). Different publications have shown that the proximal reaching of reflux episodes is important in triggering symptoms and the reduction of these episodes results in a reduction of reflux symptoms (14,15). Recently, a population based-study from Italy reported a higher prevalence and severity of esophagitis among those with more frequent reflux symptoms (16). Johnson et al. in a post-hoc analysis of five clinical trials have demonstrated that the prevalence of severe esophagitis was the highest among patients with severe heartburn. Furthermore, severe heartburn was a good clinical indicator of the presence of severe esophagitis in elderly patients, but a less reliable marker among younger patients (17). Previous evidences obtained from epidemiological and treatment trials indicate a significant association between GERD and extraesophageal symptoms (18-20). Within the ProGERD study, about 35% of the patients with erosive reflux disease had extraesophageal symptoms (20), whereas Raiha et al. found the extraesophageal symptoms in 57% of elderly patients with erosive esophagitis (21). In the same line, the present study found the extraesophageal symptoms in about 34% of the patients with any grade of erosive esophagitis and in 55% of the patients with severe GERD (grade C/D), with a significant difference. Chronic cough, as an important extraesophageal symptom, was significantly more common (about 44%) among patients diagnosed with severe GERD. This association is

supported by previous studies which have suggested a significant relationship between chronic cough and erosive esophagitis (20,22). Therefore, the upper gastrointestinal endoscopy should be part of the evaluation in the patients with suspected reflux-related chronic cough and throat symptoms (23). Despite the evidence of several epidemiological studies that GERD is associated with various esophageal and extraesophageal disorders (1), the pathogenesis of symptom manifestations remains unclear. One explanation for the heartburn is considered the stimulation of sensory nerve through direct contact with refluxed acid (24). Also, previous studies have found that the number of volume and acid reflux episode are important in reflux-esophageal lesions (13,25). Animal studies have reported that the combination of gastric content and bile acids is very injurious to the larynx, whereas human studies demonstrated that acid exposure reaching proximal esophagus is significantly increased in patients with laryngeal disorders (26). The presence of GERD symptoms in the absence of endoscopic signs of esophageal mucosal break suggests that factors other than acid reflux, such as esophageal mucosal sensitivity, abnormal esophageal contraction, and psychological factors may cause reflux symptoms (27). The present study investigated for the first time the prevalence and severity of gastroesophageal and extraesophageal symptoms in patients with GERD in Albania. Other strengths of our study were the recruitment of unselected, consecutive patients and the use of endoscopy. Furthermore, the upper endoscopy is conducted by one experienced endoscopist and assessment of symptoms is done by one physician. Despite its contribution, we are aware of potential limitations of the current study. The study limitations include the cross-sectional design, the relatively small sample size, recruitment procedure from one hospital only, and the lack of a control group. In addition, the true prevalence of extraesophageal symptoms and the relationship with GERD is difficult to assess because indivi-

duals may exhibit two independent diseases (26). In conclusion, we showed that the prevalence of esophageal and extraesophageal symptoms were higher among patients with severe reflux esophagitis. In the future, prospective clinical studies in multiple

medical centers are warranted to generalize our findings in the overall Albanian population. Further researches are needed to determine the relationship between different GERD categories and extra-esophageal symptoms.

Conflicts of interest: None declared.

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