

The association between gastroesophageal flap valve function and gastroesophageal reflux symptoms

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Abstract

Background and study aims : Upper gastrointestinal endoscopic examination is usually the first step in the evaluation of patients with suspected gastroesophageal reflux disease. The primary aim of this study was to investigate the association between gastroesophageal flap valve function (GEFV) and gastroesophageal reflux symptoms in patients undergoing routine upper endoscopy.

Patients and methods: 1507 patients were included into the study and the GEFV graded I to IV as follows: Hill I-II: normal GEFV, and Hill III-IV: abnormal GEFV.

Results : Patients in abnormal GEFV group had a higher incidence of reflux symptoms compared to normal GEFV group (53.4% vs 47.4% for heartburn $p = 0.03$ and 53.2% vs 42.4% for regurgitation, $p < 0.01$). In abnormal GEFV patients, esophagitis was more common compared to those with normal GEFV (32.6% vs 11.1%, $p < 0.01$). Presence of heartburn and regurgitation ($n = 556$) correlated with Hill III-IV grades ($n = 184/556$), (sensitivity: 33%, $p = 0.003$). In contrast, 24.6% (157/638) of patients without reflux symptoms were in abnormal GEFV group. In patients undergoing endoscopy because of reflux symptoms, Grade III-IV valve was detected more commonly in patients with reflux symptoms compared to patients without reflux symptoms ($p = 0.01$).

Conclusions : Patients with abnormal valves (Hill grades III & IV) but without reflux symptoms, esophagitis and hiatal hernia should be evaluated individually by means of the presence of gastroesophageal reflux disease which means that GEFV is not a good indicator of reflux disease. (*Acta gastroenterol belg.*, 2017, 80, 471-475).

Key words : gastroesophageal reflux, gastroesophageal flap valve, Hill classification.

Introduction

Gastroesophageal reflux disease (GERD) is characterized by the reflux of stomach contents into the esophagus which causes disturbing symptoms such as heartburn and acid regurgitation, or complications that can be attributable to reflux disease such as esophagitis, or both (1). Reflux esophagitis includes a group of patients with symptoms of GERD who also have endoscopic or histopathologic manifestations of esophageal inflammation. Indeed, 50% to 85% of patients with GERD have nonerosive reflux disease (2). The cardinal symptoms of GERD are heartburn and regurgitation. The diagnosis of GERD can be made depending upon clinical symptoms alone, and in patients with any of the clinical manifestations including heartburn and regurgitation, a presumptive diagnosis of GERD is reasonable. According to a guideline

published by American Gastroenterology Association, endoscopy with biopsy should be reserved for patients with dysphagia and patients who have not responded to an empirical therapy of proton pump inhibitors (PPIs) (3). In most patients with typical GERD symptoms, such as heartburn or regurgitation, an initial trial of empirical acid-suppressive therapy with once-daily PPIs is asserted and endoscopy is not indicated (3). However, in clinical practice when patients with heartburn and/or regurgitation visit the clinics, the first diagnostic test performed is an endoscopic examination of the upper gastrointestinal system. When esophagitis on the lower portion of the esophagus is present, diagnosis of GERD is confirmed. It has been reported that during endoscopic examination, the appearance of gastroesophageal flap valve (GEFV) gives important information such as higher Hill grades are related with lower esophageal sphincter pressure and increased prevalence of hiatal hernia (4,5). On the other hand, lower esophageal sphincter incompetency is commonly reported in patients undergoing upper gastrointestinal endoscopy for indications other than GERD. In clinical practice, once endoscopic examination has been performed and in the presence of GEFV dysfunction, PPI therapy is often initiated.

Although the appearance of GEFV gives valuable information in GERD patients, it is not clear whether it reflects GERD in patients without heartburn and regurgitation. Therefore, the primary aim of this study was to investigate the association between GEFV function in patients undergoing upper endoscopy for various indications with and without GERD symptoms. The secondary aim of this study was to explore the factors that might affect GEFV function such as age, gender, esophagitis, hiatal hernia, body mass index (BMI) and *Helicobacter pylori*.

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Patients, materials and methods

Patients

This study included an unselected group of consecutive patients who had been referred for upper endoscopy in elective conditions and who were willing to participate into the study. Exclusion criteria were as follows: presence of esophageal or gastric malignancy, esophageal or gastric varices, previous esophageal or gastric surgery and patients using mucosa protective agents (PPIs, H₂ receptor blockers etc) and medications that might affect esophageal motility. The study protocol was approved by the local ethics committee of the related institution.

Symptom assessment

Before endoscopic examination, patients were asked whether they had experienced at least one episode of heartburn or regurgitation per week regardless of severity during the last 6 months (6). Along with demographic characteristics, BMI, smoking and alcohol habits, and use of PPIs were also recorded.

Endoscopic assessment

At endoscopy, along with the assessment for the presence of esophagitis (Los Angeles classification) and hiatal hernia (extension of the gastric mucosa above the crural diaphragm more than 2 cm in the axial length), the appearance of the gastroesophageal region was evaluated while the scope in retroflexed position and the patients were classified into four categories according to the Hill's classification (7). In this classification, Grade I : prominent fold of tissue along the lesser curvature of the cardia is seen, Grade II : fold is prominent but there would be abrupt opening and closing periods around the scope, Grade III : fold is not obvious and the scope is not grasped tightly by the ridge, and Grade IV : there is no fold and squamous epithelium of the esophagus was seen easily from below and lumen of the esophagus is open. Patients were then stratified into two groups according to Hill grades : gastroesophageal flap valve function was considered normal for grades I&II (Group A) and abnormal for grades III&IV (Group B).

Statistical analysis

Statistical analysis was performed with statistical program SPSS ver. 16 for Windows (SPSS, Chicago, IL). All values were expressed as mean \pm standard deviation (SD) unless otherwise stated. Kolmogorov-Smirnov test was used for test of normality. The chi-square test was used for categorical data. Continuous non-parametric variables were analysed by using Mann-Whitney U and Kruskal-Wallis tests. The risk factors were detected by logistic regression analysis and Odds ratio (OR) with

95% confidence interval (CI) was calculated for this analysis. A *P* value less than 0.05 was considered as significant.

Results

Patient Characteristics

A total of 1507 patients were included into the study (886 women/621 man). Median age was 49 (15-88) years. Endoscopy was performed in elective conditions with various indications. Demographic characteristics, symptoms and clinical findings were illustrated in Table 1. Dyspepsia and abdominal pain is the most common indication of the upper gastrointestinal endoscopy in our patients (33.6%). Other common causes of the upper gastrointestinal endoscopy were vitamin B₁₂ and iron deficiency anemia (23.8%) and reflux symptoms (19.6%). Endoscopy was performed in some patients for only screening and check-up purposes (16.0%). Less common indications were nausea, vomiting and chronic diarrhea. Proportion of cigarette smokers was 19.6% and 5.5% of patients were using alcohol. Endoscopy was performed without sedation in 81% of the patients. According to Hill classification, 1066 patients (%70.7) had normal (Hill 1-2) GEFV function and 441 patients (%29.3) had abnormal (Hill 3-4) GEFV. When questioned; 638 patients (42.3%) had no reflux symptoms, 313 (20.8%) described any one of regurgitation or heartburn and 556 (36.9) had both symptoms of reflux. One hundred ninety three patients had various co-morbidities. Mean BMI was 27.2 \pm 5.4 kg/m² and *Helicobacter pylori* was detected in 41.6% of patients.

Relationship between Hill grading and age, gender, and body mass index

The number of male patients was significantly greater in abnormal GEFV group than in normal GEFV group (46.9% vs 36.3%, *p*<0.001). Median age was 50 (17-88) in patients with normal GEFV function and 47 (15-86) in patients with abnormal GEFV function (*p* = 0.07). Although median age did not differ between groups, it was shown that abnormal GEFV was more commonly seen in patients under age 40 (34.6% vs 27.3%; *p* = 0.003). Cigarette smoking was more common in patients with abnormal GEFV than in patients with normal GEFV (%23.5 vs 18.1% ; *p* = 0.01). Cigarette smoking was more common in male patients (*p*<0.001). Alcohol use did not differ between groups (*p* = 0.66). Median BMI in abnormal GEFV group was significantly lower than in normal GEFV group (27.3 kg/m² vs 26.0 kg/m² ; *p*<0.001). BMI differs significantly between male and female patients (26.2 kg/m² vs 27.9 kg/m² ; *p*<0.001). Because of the gender effect on these variables, we performed binary regression analysis for age, gender, cigarette smoking and BMI. Findings from this analysis demonstrated an association between male

Table 1. — Demographic characteristics and clinical features of patients studied

	Normal GEFV (Hill grade I-II)	Abnormal GEFV (Hill grade III-IV)	p
Age (years)	50 (17-88)	47 (15-86)	0.07
Gender	387M/679F	234M/207F	<0.01
Heartburn	47.4% (505/1065)	53.4% (235/440)	0.03
Regurgitation	42.4% (451/1064)	53.2% (234/440)	<0.01
Esophagitis	11.0% (117/1063)	32.3% (141/437)	<0.01
Hiatal hernia	3.5% (37/1062)	19.9% (87/437)	<0.01
Smoking	18.1% (192/1062)	23.5% (103/439)	0.01
Alcohol	5.4% (57/1062)	5.9% (26/439)	0.66
Helicobacter pylori positivity	41.7% (436/1046)	41.9% (182/434)	0.92
BMI (kg/m ²)	27.5+/-5.7	26.5+/-5.0	<0.01

Table 2. — The association between the presence of reflux symptoms and Hill grading

Reflux symptoms	Hill 1-2 (group A)	Hill 3-4 (group B)	
Regurgitation + heartburn	372 (66.9%)	184 (33.1%)	p= 0.001
Regurgitation or heartburn	213 (68.1%)	100 (31.9%)	
No reflux symptom	481 (75.4%)	157 (24.6%)	

gender and abnormal GEFV function [OR : 1.88 ; 95% CI(1.49-2.38)]. Significant association was not detected between age- cigarette smoking- BMI and abnormal GEFV function. *Helicobacter pylori* positivity on biopsy samples was not significantly different between groups.

Relationship between Hill grading and presence of reflux symptoms and esophagitis

Heartburn and regurgitation, suggestive symptoms of gastroesophageal reflux, were more commonly reported in patients with abnormal GEFV (p = 0.03 and p<0.01 respectively). In 33% of patients who describe both reflux symptoms, Hill grade 3-4 was reported. This rate was 31.9% and 24.6% in patients with describing only one symptom and no reflux symptom respectively (p = 0.003). According to our analysis, Hill grading can predict reflux symptoms with a sensitivity of 32% (95% CI ; 29%-35%) and specificity of 75% (95%CI ; 71%-78%) (Table 2). Esophagitis was present in 11% (117/1063) of patients with normal GEFV and 32.2% (141/437) of patients who had abnormal GEFV (p<0.01). Hiatal hernia was noted in 124 patients (3.3% in normal GEFV group vs 25.2% in abnormal GEFV group; p<0.01). By multivariate logistic regression analysis, it was shown that the presence of esophagitis was associated with abnormal GEFV function (OR : 3.84 CI 95%:2.90-5.09) and cigarette smoking (OR : 1.63 CI 95% : 1.18-2.25).

Discussion

GERD is one of the most prevalent diseases of the GI tract in Western countries (8). Dysfunction of the antireflux barrier is considered main reason in GERD pathogenesis. GEFV, firstly described by Hill et al in 1996, plays an important role in the prevention of pathologic reflux by creating a flap valve at the esophagogastric junction (9). Retroflex grading of GEFV during upper GI endoscopy is simple and not time consuming and it provides useful information to the endoscopist about the status of a patient with GERD. GEFV was graded from 1 to 4 using Hill classification. GEFV 1-2 was considered normal and 3-4 abnormal. In this study, GEFV functions have been studied in a large number of patients. Relationship between GEFV Hill grading and age-gender-cigarette smoking-alcohol usage- *Helicobacter pylori* positivity was examined. In this study, patients with normal and abnormal GEFV did not show significant differences in age (p = 0.07), but in patients under the age of 40 incidence of abnormal GEFV was found more frequent than those over the age of 40 (34.6% vs 27.3% p = 0.003). Similar findings were observed in another study (10). In patients with abnormal GEFV, 53% of the patients were male while this was 36% in patients with normal GEFV (p<0.01). Male predominance in patients with abnormal GEFV has also been found in other studies (4,11,12). In our patient group, cigarette smoking was significantly more common in males (p<0.01) and the proportion of patients who smoke cigarette was higher in abnormal GEFV group (18.1% vs 23.5%, p = 0.01). Body mass index was significantly low in the abnormal GEFV group and there is male predominance in abnormal GEFV group. However, role of gender factors should be taken into account because body mass index was higher in females in our patient group. Eventually, binary logistic regression analysis showed male gender was significantly associated with abnormal GEFV function [OR : 1.88 95% CI : (1.4-2.38) ; p<0.001]. Age, smoking and BMI were not found to be associated with abnormal GEFV function in this multivariate analysis. Any cor-

relation between GERD symptoms (regurgitation and heartburn) and Hill grading, which is a controversial topic in the literature, was also analyzed in detail. Our study showed that patients with Hill grade 3-4 were more likely to have GERD symptoms and esophagitis and hiatal hernia were detected significantly more frequent in these patients. In normal GEFV group, both reflux symptoms (regurgitation and/or heartburn) were present in 34.8% of the patients. It may be suggested that, in these patients, other factors (dysfunction of other components of esophagogastric junction, esophageal body dysfunction, delayed gastric emptying, increased intragastric pressure, esophageal hypersensitivity) contribute to the development of GERD symptoms (13). Although reflux symptoms detected more common in patients with abnormal Hill grade, Hill grading had a low sensitivity and high specificity to determine whether the presence or absence of reflux symptoms in our study. Previous studies showed positive correlation between Hill grading and reflux symptoms and presence of esophagitis (4,6,11,12,14-18). Frequency of esophagitis and hiatal hernia was also studied in our study. We found that esophagitis was more common in abnormal GEFV patients (11.1% vs 32.6% ; $p < 0.01$) and not only grade 2-3 esophagitis but also grade I esophagitis was significantly more frequent in abnormal GEFV patients. By multivariate logistic regression analysis, abnormal GEFV and cigarette smoking were found to be related with the presence of esophagitis in our study (OR : 3.84 and OR : 1.63 respectively). Hiatal hernia were found to be significantly more common in patients with abnormal GEFV (3.5% vs 19.9% ; $p < 0.001$). In a previous study, it was found that GEFV grading can predict the size of hiatal hernia (14). These findings indicate that abnormal GEFV may suggest the severity of GERD. Proton pump inhibitor therapy is effective in the treatment of reflux symptoms and esophagitis. GEFV grading was found to be useful as prognostic determinant of on-demand PPI therapy of GERD (16). GEFV may be reported as normal in some GERD patients and abnormal in some patients who have not GERD. In this context, it is not appropriate initiating PPI therapy just looking at the GEFV status of patients. There are some studies showing the association between higher Hill grades and the frequency of GERD (4,14). It has also been shown that higher Hill grades are associated with lower LES pressure and increased prevalence of hiatal hernia (4,5). Patients with higher Hill grades have poor response to proton pump inhibitor treatment (19). Finally, Hansdotter et al measured the axial length of the hiatal hernia and evaluated the GEFV status of 334 individuals in order to compare the two endoscopic grading methods with regard to associations with GERD (20). Their study did not verify that Hill grading was not superior to measuring axial length of a hernia and concluded that using Hill grading is a reasonable choice instead of measuring axial length of a hernia in the evaluation of anti-reflux barrier due to the difficulty of endoscopic measurement of axial hiatal

hernia. There are some limitations of this study. First, this was a single center study, and reliance on only patients' symptoms may introduce bias. Second, the esophageal manometry and ambulatory pH monitoring studies were not performed in the majority of patients which might be useful in the discrimination of real reflux patients.

In conclusion, GEFV function plays an important role in the development of reflux. However, a significant portion of patients with reflux symptoms has normal GEFV function. Probably other factors take a dominant role in the development of reflux symptoms in these patients. According to our findings, GEFV grading gives useful information about GERD status but is not a sensitive method for the prediction of reflux symptoms. Eventually, when making treatment decision, we should take into account not only GEFV status but also clinical findings of patients.

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Information on Ethics Committee Approval

This study was approved by the Institutional Review Board of Ankara University Faculty of Medicine (date: 12.01.2015, #01-19-15).

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