Turk J Gastroenterol 2008; 19 (3): 145-151

Low prevalence of erosive esophagitis and Barrett esophagus in a tertiary referral center in Turkey

Tersiyer bir referans merkezinde eroziv özofajit ve Barett özofagusunun düşük prevalansı

Berna BAYRAKÇI[1], Elmas KASAP[1], Gül KİTAPÇIOĞLU[2], Serhat BOR[1]

Departments of [1]Gastroenterology and [2]Public Health, Ege University, School of Medicine, İzmir

Background/aims: *The purpose of upper gastrointestinal endoscopy in gastroesophageal reflux disease is to detect the complications; both Barrett esophagus and erosive esophagitis are common in developed countries. We aimed to investigate the ratio of esophageal complications in gastroesophageal reflux disease and the relationship between reflux symptoms and erosive esophagitis.* ***Methods:*** *Six hundred forty-five consecutive adult patients presenting to the Reflux Outpatient Clinic were evaluated prospectively. One hundred sixty patients who underwent upper gastrointestinal endoscopy and who complained of heartburn or regurgitation occurring at least weekly were selected. The complaints and general features of patients were queried via a detailed questionnaire.* ***Results:*** *Twenty-seven patients (17%) had endoscopic evidence of erosive esophagitis. Barrett esophagus was found in 3 patients (2%). Neither esophageal stricture nor adenocarcinoma was found. Esophagitis was low grade (grades A and B) in 25 of the 27 (92%) with erosive esophagitis. Patients with erosive esophagitis consumed less alcohol than patients with non-erosive reflux disease. No difference was found between the severity of symptoms in patients with erosive esophagitis and non-erosive reflux disease.* ***Conclusions:*** *Barrett esophagus and erosive esophagitis were less common compared to the literature although the study was conducted in a tertiary reference center for gastroesophageal reflux disease. The presence of severe symptoms in gastroesophageal reflux disease is not an indication for upper gastrointestinal endoscopy. No impact of Helicobacter pylori on the severity of esophagitis or symptoms was shown.*

Key words: Gastroesophageal reflux disease, Barrett esophagus, endoscopy, erosive esophagitis, non-erosive reflux disease, prevalence, *Helicobacter pylori*

Amaç: *Gastroözofageal reflü hastalığında üst gastrointestinal sistem endoskopisinin amacı komplikasyonları saptamaktır. Hem Barett özofagus hem de eroziv özofajit gelişmiş ülkelerde yaygındır. Biz bu çalışmada gastroözofageal reflü hastalığının özofageal komplikasyonlarının oranını ve reflü semptomlarıyla eroziv özofajit arasındaki ilişkiyi incelemeyi amaçladık.* ***Yöntem:*** *Reflü polikliniğine başvuran ardışık 645 yetişkin hasta prospektif olarak değerlendirildi. Üst gastrointestinal sistem endoskopisi yapılan ve en az haftada bir pyrozis veya regurjitasyonu olan / 160 hasta seçildi. Hastaların şikayetleri ve genel özellikleri detaylı bir anketle sorgulandı.* ***Bulgular:*** *27 hasta (%17) eroziv özofajitin endoskopik bulgularına sahipti. Barett özofagus 3 hastada (%2) saptandı. Ne özofageal striktür ne de adenokarsinom mevcut değildi. Eroziv özofajit olan hastaların 25'i (%92) düşük derece (derece A ve B) özofajitti. Eroziv özofajitli hastalar noneroziv reflü hastalığı olanlardan daha az alkol tüketimine sahipti. Eroziv özofajit ve noneroziv özofajiti olan hastaların arasında semptomların şiddeti açısından herhangi bir fark saptanmadı.* ***Sonuç:*** *Bu çalışma gastroözofageal reflü hastalığı için dördüncü referans merkezinde yapılmasına rağmen, Barett özofagus ve eroziv özofajit literatürle karşılaştırıldığında daha az yaygınlıkta görülmüştür. Gastroözofageal reflü hastalığında şiddetli semptomların varlığı üst gastrointestinal sistem endoskopisi için endikasyon oluşturmaz. Özofajit veya semptomların şiddeti üzerine Helikobakter pylorinin etkisi gösterilememiştir.*

Anahtar kelimeler: Gastroözofageal reflü hastalığı, Barett özofagus, endoskopi, eroziv özofajit, noneroziv özofajit, prevelans, *Helikobakter pylori*

INTRODUCTION

Prevalence of gastroesophageal reflux disease (GERD) is high, especially in the developed countries. GERD is considered the most common chronic disease in the United States (1). When GERD is defined as presence of at least one of either heartburn or regurgitation once a week or more often, its community-based prevalence is 19.8%. Prevalence of GERD was estimated as 20% in a study conducted by Bor et al. (2) in Izmir and as 22.8% in the study of the same group in the whole country, similar to the rates in the US.

Complications of GERD include erosion-ulceration, hemorrhage, stricture, and Barrett esophagus (BE) (3). GERD and BE are risk factors for esophageal adenocarcinoma. Endoscopy is an invasive procedure and thus symptoms and signs are being

Address for correspondence: Serhat BOR
Ege Üniversitesi Tıp Fakültesi
Gastroenteroloji B.D. İzmir, Turkey
Phone: +90 232 373 15 47
E-mail: serhat.bor@ege.edu.tr

Manuscript received: 05.02.2007 **Accepted:** 10.01.2008

sought to better predict complications of GERD. Findings from the studies performed so far have been contradictory. Endoscopic findings in patients with GERD have ranged as widely as from 10% to 70% and, interestingly, these findings have been recorded even in 8% of asymptomatic individuals (4).

Turkey is an interesting area, showing a high prevalence of GERD and *Helicobacter pylori (H. pylori),* and the relationship between these two parameters is not fully understood. Some of the retrospective studies and our observations demonstrate that prevalence rates of erosive esophagitis (EE) and BE are low in the country (5). Nevertheless, a study from Ankara reported BE at rates similar to those reported from western countries (6). Moreover, a study from our country in which 4065 patients were studied retrospectively in 16 centers reported that stomach adenocarcinomas did not change location from distal to proximal over the period 1990-2000, in contrast to the findings from developed countries (7). This finding indirectly suggests that prevalence of BE in Turkey should be lower than in developed countries.

For these reasons, a study correlated with upper gastrointestinal (GI) endoscopy and histopathology was planned in which symptoms of the patients with GERD undergoing endoscopic examination were evaluated in detail. The vast majority of the subjects included in the current study are those referred from other centers to the Reflux Outpatient Clinic, Section of Gastroenterology, Ege University Medical School. This Outpatient Clinic is the only one specialized in this disease in our country. Prevalence rates in the previous retrospective study of BE and EE were found to be low, thus requiring a detailed prospective study, although the findings of the current study carry the risk of reflecting only the most severe cases (5).

MATERIALS AND METHODS

Patient Selection

Six hundred forty-five consecutive adult patients presenting to the Reflux Outpatient Clinic, Section of Gastroenterology, Ege University Medical School between 1 April 2004 and 1 March 2005 were evaluated prospectively. Indications of upper GI endoscopy in the patients presenting to the Reflux Outpatient Clinic were as follows:

a. Age over 50 or presence of reflux complaints for at least five years.

b. Presence of alarm findings such as dysphagia, odynophagia, unexplained weight loss, and anemia, etc.

c. Having referred to the Reflux Outpatient Clinic upon considering BE in the investigations performed at other centers.

d. Presence of complaints after anti-reflux surgery.

Among the patients undergoing endoscopy, those in whom heartburn and/or regurgitation were experienced once a week or more often were included in the study.

The exclusion criteria were as follows:

1. Not completing or incompletely filling the survey form of the Reflux Outpatient Clinic.

2. Performance of upper GI endoscopy outside our department and no necessity to repeat the endoscopic examination.

3. Presence of reflux from lesions of gastric outlet (i.e., stomach carcinoma).

4. Barrett surveillance endoscopies.

GERD Questionnaire

Data ascertained from all patients via the survey form included their height and weight; educational status; smoking and alcohol consumption; presence, frequency and severity of heartburn, regurgitation, non-cardiac chest pain (NCCP) and dysphagia; presence of odynophagia, dyspepsia, chronic pharyngitis, laryngitis and asthma; frequency of visits to the physician; as well as any treatment received with respect to acid-inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and eradication therapy for *H. pylori.* This questionnaire was validated previously and contained detailed information (8). The scoring system for heartburn and regurgitation is shown in Table 1.

Table 1. Scoring of heartburn and regurgitation

		Score
Duration	≤1 year	1
	1-5 years	2
	5-10 years	3
	>10 years	4
Frequency	Less than once a month	1
	Once a month	2
	Once a week	3
	Daily	4
Severity	Mild	1
	Moderate	2
	Severe	3
	Very severe	4

Minimum score: 0, Maximum score: 12.

Reflux score, the reliability of which was shown in previous studies, was used after modification for evaluation of GERD symptoms (Table 2).

Upper Gastrointestinal Endoscopy

Diagnostic criterion for endoscopic EE was presence of one or more mucosal injury at the distal esophagus on endoscopy (erosion or ulceration). Los Angeles classification was used in evaluation of the patients with erosive distal esophagitis (9). Detecting normal distal esophageal findings despite reflux signs was defined as non-erosive distal esophagitis (10). Columnar epithelium on the distal esophagus observed to rise proximally from the gastric plications and intestinal metaplasia and/or goblet cells found in biopsy samples with Alcian-blue staining (pH: 2.5) from these sites was considered as diagnostic criterion for BE. Presence of specialized intestinal epithelium on the anatomical gastroesophageal junction on a segment of more than 3 cm was called long-segment BE and on a segment of less than 3 cm was called short-segment BE. The diagnosis of hiatal hernia was confirmed by the presence of gastric folds ≥3 cm above the diaphragmatic hiatus. Three groups (2 specimens from each group) of routine biopsies were obtained from all patients: antrum, body and esophagus (3 cm above the Z-line). In the case of BE, four quadrant biopsies were obtained from the top of the gastric folds to the Z-line for every 2 cm.

Table 2. Reflux scoring

Symptom	Frequency	Score
Heartburn	Daily	3
	At least once per week	2
	At least once per month	1
	Never	0
Regurgitation	Daily	3
	At least once per week	2
	At least once per month	1
	Never	0
Non-cardiac chest pain	Daily	3
	At least per week	2
	At least once per month	1
	Never	0
Dysphagia	Daily	3
	At least once per week	2
	At least once per month	1
	Never	0
Dyspepsia	Yes	1
	No	0
Cough	Yes	1
	No	0
Hoarseness	Yes	1
	No	0
Dyspnea	Yes	1
	No	0

Minimum score: 0 Maximum score: 16

Presence of *H. pylori* was investigated by histological examination of the samples from the antrum and/or corpus.

Based on the endoscopic findings, the patients were divided into three groups as those with erosive- or non-erosive esophagitis and BE.

Statistical Analysis

Statistical analyses were done using SPSS and Graft ped softwares (SPSS 11.5 for Windows, Graft ped 4.0). t test was used for parametric comparisons and chi-square (X^2) and Fisher's exact test for categorical comparisons. Welch correction was applied when variances of the groups were different on chi-square test. P values less than 0.05 were considered as statistically significant.

RESULTS

The Reflux Outpatient Clinic of Ege University School of Medicine, Section of Gastroenterology, is the first and specific outpatient clinic for GERD patients in the country and is the referral center for 16 million of the Aegean area population. Six hundred forty-five consecutive adult patients presenting to this Clinic between 1 April 2004 and 1 March 2005 were evaluated prospectively. Two hundred twenty-two of these cases had undergone upper GI endoscopy. Thirty-four patients with heartburn and regurgitation less often than once weekly and 28 patients with missing data on the questionnaires were excluded from the study. Accordingly, 160 patients were included in the study. Mean age of the patients was 48 ± 11.4 years (median: 50, range: 19–79). Sixty-four cases (40%) were male and 96 (60%) female. One hundred twenty-two of the cases (76%) had previously sought medical advice for GERD.

Distribution of symptoms of the patients is shown in Table 3. As shown in our previous community-based studies, the most common symptom was regurgitation (2). Additionally, when the patients were asked as to which of their symptoms was most frequent, 39.4% of them emphasized regurgitation. It was remarkable that concomitant symptoms were very frequent. Mean heartburn score was 6.7 ± 3.3 (median: 7; range: 0–12), mean regurgitation score 7.7 ± 2.4 (8; 0–12) and mean reflux score 7.4 ± 2.8 (7; 2–14).

Ninety-six patients (60%) had been on NSAIDs or aspirin over the last year and 148 patients (92.5%) were receiving treatment with acid-inhibitors. Fifty-seven patients (35.6%) did not remember

whether they had *H. pylori* eradication, 48 (30%) stated that they had received eradication treatment, and 55 (34.4%) stated that they had not received eradication treatment.

Table 3. Distribution of symptoms among patients with GERD

Parameter	Number	%
Heartburn	135	84.4
Regurgitation	151	94.4
Non-cardiac chest pain	100	62.5
Dysphagia	97	60.6
Odynophagia	38	23.8
Dyspepsia	127	79.4
Bleeding	7	4.4
Cough	62	38.8
Asthma	22	13.8
Hoarseness	40	25
Chronic pharyngitis/laryngitis	77	48.1

Upper Gastrointestinal Endoscopies and Pathological Findings

Erosive esophagitis was found in 27 patients (17%). Fourteen (51%) of the EE cases were grade A, 11 (41%) grade B, 1 (4%) grade C and 1 (4%) grade D. BE was found in only 3 patients (2%) and all of these were of short-segment type (Figures 1, 2). While no metaplasia was found in 2 patients, 1 of these patients was referred for argon plasma coagulation upon finding high-grade dysplasia proven by repeated biopsies. No esophageal stricture or adenocarcinoma was found. Hiatus hernia was detected in 29 patients (18%).

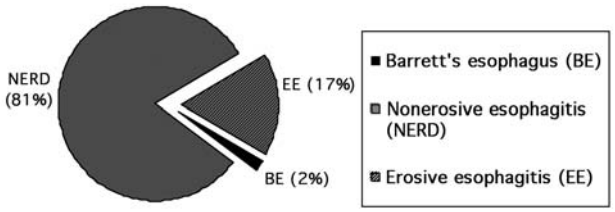

Figure 1. Endoscopic findings of the esophagus.

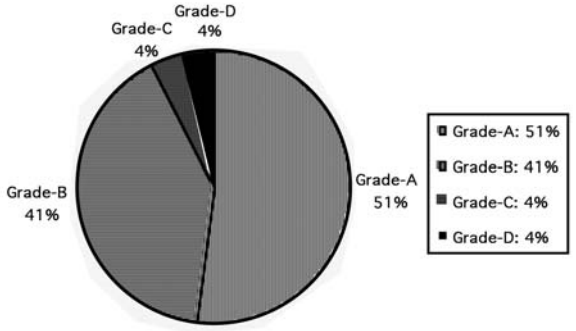

Figure 2. Grades of erosive esophagitis according to Los Angeles classification.

On endoscopic examination, findings were: normal in 32 patients (20%), pangastritis in 24 (15%), antral gastritis in 68 (42%), atrophic gastritis in 11 (7%), bulbitis in 23 (14%), duodenal ulcer in 6 (4%), fundoplication surgery in 2 (1.2%), and Billroth I procedure in 4 (2.5%). One hundred thirty-nine patients had undergone antral biopsy, and intestinal metaplasia was found in 15 (10%) of these biopsies. Presence of *H. pylori* was investigated in 135 patients by histological examination of the samples from the antrum and/or corpus and was found in 61 (45%) of these patients.

Comparison of the Patients with Erosive and Non-Erosive Esophagitis

Demographic characteristics of the groups of erosive and non-erosive esophagitis are shown in Table 4. The only significant difference between the two groups was alcohol consumption, with alcohol being used by 7% of those with EE and by 32% of those with non-erosive esophagitis (p=0.009). There was no significant difference in clinical findings between the two groups (Table 5). Reflux score was estimated to be 7.3 ± 2.6 in the patients with EE and 7.4 ± 2.8 in those with non-erosive esophagitis (p=0.89). Hiatus hernia was found in 30% of the patients with EE (n = 8) and 16% of the patients with non-erosive esophagitis (p=0.09). H. pylori infection was investigated in 23 patients with EE and in 110 patients with non-erosive esophagitis and was found in 50% (n = 11) of those with EE and 43% (n = 47) of those with non-erosive esophagitis (p=0.65). Gastric intestinal metaplasia was found in 4% (n = 1) of the patients with EE and in 12% (n=13) of the patients with non-erosive esophagitis (p=0.47). No statistically significant relationship was found between the presence of *H. pylori* infection and dyspepsia, heartburn score and regurgitation score.

DISCUSSION

Barrett esophagus and erosive esophagitis are common complications of GERD in western countries. However, eastern countries represent different risk factors for GERD such as eating habits, lower prevalence of obesity, high rate of *H. pylori,* and low parietal cell mass, etc. For these reasons,

the prevalence of these complications might be different in developing and under-developed countries and thus more data are needed.

An interesting finding in the study is the low prevalence of EE (17%) and BE (2%) in this tertiary referral center in a high GERD prevalence area. No patient was seen with esophageal stricture or adenocarcinoma. Studies from western countries have unanimously showed a high prevalence of EE. In a study by Votilainen et al. (11) from Finland, EE, esophageal stricture and BE were found in 62%, 1% and 4%, respectively, of the patients with GERD symptoms, and 27% of these patients ingested antacids, H2-receptor antagonists (H2Ra), proton pump inhibitors (PPIs) or sucralfate. Mantynen et al. (11) from Finland found EE, esophageal stricture and BE at the rates of 33.4%, 0.1% and 1.4%, respectively. One patient with esophageal adenocarcinoma was detected and 13% of patients ingested acid-inhibitor therapy (12). Similarly, EE was found in 49% of the patients in another study by Garrido Serrano et al. (13) from Spain, and these patients did not use acid-inhibitor therapy. In a study by Wo et al. (14) from the United States, EE, esophageal stricture and BE were found in 41%, 22% and 6% of cases, respectively, on upper GI endoscopies for alarm symptoms in the patients with GERD, whereas these conditions were found in 34%, 2% and 16%, respectively, on upper GI endoscopies for persistent heartburn. In the first group, 57% of patients used acid-inhibitor therapy, while in the second group, all the patients used acid-inhibitor therapy. No cancer was found. In another study by Blustein et al. (4) from Canada, EE, esophageal stricture and BE were found at the rates of 60%, 8% and 6%, respectively, without any adenocarcinoma. Sixty-eight percent of these patients took antacid therapy.

One thousand patients without acid-inhibitor therapy referred for endoscopy were studied by Rosaida (15) from Malaysia, and 13.4% and 2% of patients had endoscopic reflux esophagitis and BE, respectively. Most of the patients with EE (80%) had grades A and B EE. Three hundred and thirty-two patients in this study had GERD. In patients with GERD, EE was found in 23%. Okamoto (16) from Japan screened 8031 patients without therapy with GI symptoms and found grades A and B esophagitis in 13.1% and grades C and D in 1.8%. Furthermore, in patients with GERD, EE was found in 20%. As in these studies, the patients with EE in the current study had mild esophagitis and severe esophagitis was seen rarely.

In the researches conducted in Turkey, all endoscopic findings were retrospectively evaluated. EE and BE were detected in 8-16% and 1.5%, respectively (17-19). In a study by Mungan et al. (19), 585 patients had been evaluated using the questionnaire. In that study, 82 patients who completed the questionnaire accepted endoscopy. Sixty-eight of 82 patients were found to have GERD symptoms. In patients with GERD symptoms, EE and BE were found in 56% and 5.6%, respectively. However, the number of patients studied was small and endoscopy was performed only in those patients that accepted it. Therefore, possibility of selection bias exists in that study.

In our study, the large number of patients ingesting acid-inhibitor therapy can be associated with the low rate of EE. EE was found 30-60% in western countries, although the patients took acid-inhibitor therapy (4, 11-13). In a study from the United States, all patients ingested acid-inhibitor therapy and 34% of them were found to have EE (14). However, in our study, 92% of patients ingested acid- inhibitor therapy and EE was found in 17%. These results suggest that EE in Turkey is relati-

Table 4. Baseline characteristics of patients with erosive esophagitis and non-erosive reflux disease

Parameter	Erosive esophagitis (n:27)	Non-erosive reflux disease (n:131)
Age (year)	51.4±13.4	48.1±11
Male (%)	52	37
Alcohol consumption (%)	7	32*
Smokers (%)	56	50
Body mass index (kg/m²)	27.8±2.8	26.4±4

*p<0.05 compared to erosive esophagitis.

Table 5. The symptoms of erosive esophagitis compared to non-erosive reflux disease

	Erosive (n:27)	Non-erosive (n:131)
>5 years heartburn (%)	48	36
>5 years regurgitation (%)	52	32
Severe or very severe heartburn (%)	26	28
Severe or very severe regurgitation (%)	41	35
Non-cardiac chest pain (%)	52	64
Dysphagia (%)	74	57
Odynophagia (%)	30	22
Cough (%)	44	38
Hoarseness (%)	33	24
Asthma (%)	7	15
Esophagopulmonary reflux (%)	44	44
Frequency score of reflux	7.3±2.6	7.4±2.8

*p<0.05 compared to erosive esophagitis.

vely less frequent than in western countries. Eastern countries also report low frequency (20%), although no acid-inhibitor therapy was used (15, 16).

A brief review of the previous research reveals that EE, esophageal stricture and BE are more frequent in Europe and America compared to Asia. Furthermore, esophageal adenocarcinoma in GERD is exceedingly rare worldwide and was not found at all in most GERD studies. The fact that EE and BE were found in low rates and that no stricture was found in our study is consistent with the studies conducted in Asia. Also consistent with previous studies, no adenocarcinoma was found. Attempts to explain these lower rates in Asia usually cited lower body mass index (BMI), differences in eating habits and genetic composition. However, BMI of all studied patients was high in these studies (BMI: 26.7). It would be more appropriate to emphasize the other two reasons for the lower rates found in the current study.

A total of 1640 consecutive patients with reflux esophagitis were studied in the Netherlands by Loffeld (20). Sixty-one patients were of Turkish descent. Reflux esophagitis occurred significantly more often in ethnically Dutch people (overall 33% vs. 9.7%, $p<0.001$). *H. pylori* was present in 60.6% of Turkish patients and in 18.5% of Dutch patients. All Turkish patients suffered only from mild esophagitis. Similar to our findings, it was concluded that the occurrence of reflux esophagitis is low in a population of Turkish patients with a high prevalence of *H. pylori.* This study suggests that EE is less frequent in Turkish than in European patients.

While heartburn in patients with GERD undergoing upper GI endoscopy was seen at a rate of 84.4%, regurgitation was seen at a rate of 94.4% in our study. It has been shown in our population-based study that GERD is being seen with a lower incidence of heartburn and a higher incidence of regurgitation compared to the US and other developed countries (2, 21). Since regurgitation is the dominant symptom in this and our other epidemiology studies, this might be related with the high prevalence of *H. pylori* infection modifying the acid content of the refluxate (22, 23). *H. pylori*-related corpus gastritis results in acid hyposecretion; therefore, patients mainly feel the regurgitation but less so the burning feeling (volume refluxers). This relatively low amount of acid reflux may protect against the complications of GERD such as BE. In addition, and contrary to the situation in developed countries, the ratio of distal vs proximal gastric adenocarcinomas in Turkey did not change within the last 11 years (7). This might give an indirect evidence about the low prevalence of BE. However, no difference was found in patients with or without erosions. Frequency of *H. pylori* infection was found to be 45% in the current study. This figure was 74% in the community in the study by Bor et al. (2). The lower frequency of *H. pylori* infection in GERD might be related with the fact that more than half of the study population stated a previous history of *H. pylori* eradication, or it may support the opinion that it is a protective factor in GERD (18, 24-26).

Results of the studies investigating the differences between erosive and non-erosive esophagitis are inconsistent. It was concluded in the study by Votilainen et al. (11) that most of the cases less than 50 years old had no endoscopic findings, and no significant correlation was found between reflux symptoms and endoscopic findings. No relationship was found between GERD symptoms and EE in a study by Okamoto et al. (16). Serrano et al. (13) found a significant relationship between severe esophagitis and elder age, male gender, smoking and *H. pylori* negativity. In another study by Locke et al. (27), a significant relationship was found between EE and duration of regurgitation and frequency of heartburn. In the study by Rosaida (15), risk factors for EE were male gender, hiatus hernia and alcohol consumption. In the study by Labenz et al. (28), risk factors for EE were male gender, higher BMI, alcohol consumption, presence of reflux complaints for more than one year, and smoking. Fujiwara et al. (29) from Japan showed a relationship between non-erosive esophagitis and female gender, lower BMI, being a nonsmoker and absence of hiatus hernia. In our study, a significant difference was found only in alcohol consumption between the erosive and non-erosive esophagitis groups. EE was found more commonly in the cases not consuming alcohol. This may be due to these cases avoiding alcohol because of its contribution to the worsening of their symptoms.

In conclusion, non-erosive esophagitis was found more frequently; however, complications of GERD such as BE, stricture and EE were less in this study compared to the studies from developed countries. This study was conducted in a tertiary referral center and in an area in which the prevalence of GERD is as high as in developed countries. Non-erosive esophagitis is significantly more com-

mon and no significant difference was found between symptoms of the patients with erosive versus non-erosive esophagitis. Thus, severity of the symptoms does not provide us with information on whether or not to perform endoscopy, meaning that presence of severe symptoms in GERD is not an indication for upper GI endoscopy. The low prevalence of BE also indicates that data and guidelines from developed countries should be adapted carefully in developing countries.

REFERENCES

1. Locke GR III, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112: 1448-56.
2. Bor S, Mandıracıoğlu A, Kitapçıoğlu G, et al. Gastroesophageal reflux in a low-income region in Turkey. Am J Gastroenterol 2005; 100: 744-54.
3. Spechler SJ. Esophageal complications of gastroesophageal reflux disease: presentation, diagnosis, management, and outcomes. Clin Cornerstone 2003; 5: 41-8.
4. Blustein PK, Beck PL, Meddings JB, et al. The utility of endoscopy in management of patients with gastroesophageal reflux symptoms. Am J Gastroenterol 1998; 93: 2508-12.
5. Yılmaz N, Tuncer K, Alkanat M, et al. The evaluation of Barrett esophagus cases: hiatus hernia can be a reason of overdiagnosis. Turk J Gastroenterol 2001; 12 (Suppl): 60.
6. Toruner M, Soykan I, Ensari A, et al. Barrett's esophagus: prevalence and its relationship with dyspeptic symptoms. J Gastroenterol Hepatol 2004; 19: 535-40.
7. Bor S, Vardar R, Memik F, et al. Prevalence patterns of gastric cancer in Turkey: a model of a developing country with high occurrence of *Helicobacter pylori.* Gut 2002; 51, spl: 3, A 104.
8. Kitapcioglu G, Mandiracioglu A, Bor S. Psychometric and methodological characteristics of a culturally adjusted gastroesophageal reflux disease questionnaire. Dis Esophagus 2004; 17: 228-34.
9. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999; 45: 172-80.
10. [No authors listed]. An evidence-based appraisal of reflux disease management - The Genval Workshop Report. Gut 1999; 44: S1-16.
11. Voutilainen M, Sipponen P, Mecklin JP, et al. Gastroesophageal reflux disease: prevalence, clinical, endoscopy and histopathological findings in 1,128 consecutive patients referred for endoscopy due to dyspeptic and reflux symptoms. Digestion 2000; 61: 6-13.
12. Mantynen T, Farkkila M, Kunnamo I, et al. The impact of upper GI endoscopy referral volume on the diagnosis of gastroesophageal reflux disease and its complications: a 1 year cross-sectional study in a referral area with 260,000 inhabitants. Am J Gastroenterol 2002; 97: 2524-9.
13. Garrido Serrano A, Guerrero Igea FJ, Lepe Jimenez JA, Perianes Harnandez C. Clinical features and endoscopic progression of gastroesophageal reflux disease. Rev Esp Enferm Dig 2003; 95: 712-6, 107-11.
14. Wo JM, Mendez C, Harrell S, et al. Clinical impact of upper endoscopy in the management of patients with gastroesophageal reflux disease. Am J Gastroenterol 2004; 99: 2311-6.
15. Rosaida MS, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and nonerosive reflux disease in multiracial Asian population: a prospective, endoscopy based study. Eur J Gastroenterol Hepatol 2004; 16: 495-501.
16. Okamoto K, Iwakiri R, Mori M, et al. Clinical symptoms in endoscopic reflux esophagitis: evaluation in 8031 adult subjects. Dig Dis Sci 2003; 48: 2237-41.
17. Yilmaz N, Tuncer K, Tunçyurek M, et al. The prevalence of Barrett's esophagus and erosive esophagitis in a tertiary referral center in Turkey. Turk Gastroenterol 2006; 17: 79-83.
18. Unal S, Karakan T, Dogan I, et al. The influence of *Helicobacter pylori* infection on the prevalence of endoscopic erosive esophagitis. Helicobacter 2006; 11: 556-61.
19. Mungan Z, Demir K, Onur MD, et al. Characteristics of gastroesophageal reflux disease in our country. Turk Gastroenterol 1999; 10: 101-6.
20. Loffeld RJ. *H. pylori* and reflux esophagitis in Turkish patients living in the Zaanstreek region in the Netherlands. Dig Dis Sci 2003; 48: 1846-9.
21. Domestic International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol 1999; 34: Suppl 231.
22. Falk GW. The possible role of *Helicobacter pylori* in GERD. Semin Gastrointest Dis 2001; 12: 186-95.
23. Vigneri S, Termini R, Savarino V, Pace F. Review article: Is *Helicobacter pylori* status relevant in the management of GORD? Aliment Pharmacol Ther 2000; 14(Suppl): 31-42.
24. Haruma K, Hamada H, Mihara M, et al. Negative association between *Heliobacter pylori* infection and reflux esophagitis in older patients: case-control study in Japan. Helicobacter 2000; 5: 24-9.
25. Hamada H, Haruma K, Mihara M, et al. High incidence of reflux oesophagitis after eradication therapy for *Helicobacter pylori:* impacts of hiatal hernia and corpus gastritis. Aliment Pharmacol Ther 2000; 14: 729-35.
26. Zhang J, Chen XL, Wang KM, et al. Relationship of gastric *Helicobacter pylori* infection to Barrett esophagus and gastro-esophageal reflux disease in Chinese. World J Gastroenterol 2004; 10: 672-5.
27. Locke GR, Zinsmeister AR, Talley NJ. Can symptoms predict endoscopic findings in GERD? Gastrointest Endosc 2003; 58: 661-70.
28. Labenz J, Jaspersen D, Kulig M, et al. Risk factors for erosive esophagitis: a multivariate analysis on the ProGERD study initiative. Am J Gastroenterol 2004; 99: 1652-6.
29. Fujiwara Y, Higuchi K, Shiba M, et al. Differences in clinical characteristics between patients with endoscopy-negative reflux disease and erosive esophagitis in Japan. Am J Gastroenterol 2005; 100: 754-8.