

## PREVALENCE OF BARRETT'S ESOPHAGUS IN EASTERN TURKEY

ABDURRAHMAN SAHIN<sup>1</sup>, GOKHAN ARTAS<sup>2</sup>

<sup>1</sup>Department of Gastroenterology - <sup>2</sup>Department of Pathology, Firat University Faculty of Medicine, Elazig, Turkey

### ABSTRACT

**Objective:** To determine the prevalence of Barrett's Esophagus (BE) among patients undergoing esophagogastroduodenoscopy (EGD) in a tertiary care center in Eastern Turkey and to compare with the prevalences of other regions of Turkey.

**Methods:** We retrospectively reviewed the endoscopy database and consecutive adult patients who underwent an EGD for any indication between January 2015 and December 2017 were included. Cases of endoscopically suspected and biopsied were evaluated and, biopsy proven BE were identified. Gastric and esophageal endoscopic and histopathological findings were evaluated.

**Results:** A total of 8275 patients who underwent EGD, 241 patients (2.9%) had endoscopically suspected and biopsied for BE. Among them, 161 patients (1.9%) had biopsy proven BE. The mean age of the patients with BE was  $48.0 \pm 16.7$  years and only 74 patients (46%) were over 50 years. Of the 161 patients, 82 (51%) were women. Eight of them had long-segment BE (LSBE) ( $>3$  cm) while 153 had short-segment Barrett's Esophagus (SSBE) ( $\leq 3$  cm). Only seven patients had low-grade dysplasia, and none had high-grade dysplasia. A total of 111 patients (61%) were positive for *Helicobacter pylori*. Gastric intestinal metaplasia was found in 22 (14%).

**Conclusions:** The prevalence of BE in this study was found higher from other regions of Turkey. The reasons for these results should be further investigated.

**Keywords:** Barrett's esophagus, Gastroesophageal reflux disease, prevalence, Turkey.

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### Introduction

Barrett's esophagus (BE) is defined as the replacement of the metastatic columnar epithelium instead of squamous epithelium in the distal parts of the esophagus<sup>(1)</sup>. Barrett's esophagus is detected in approximately 5-15% of patients undergoing endoscopy due to gastroesophageal reflux disease (GERD), and 1-2% of all patients who undergo endoscopy for any reason<sup>(2,3)</sup>. It is the most dangerous complication of GERD. The diagnosis is made by the combination of endoscopic and histological criteria<sup>(4)</sup>.

The prevalence of BE in the unselected general population is between 1 and 2% in European studies

and approximately 5-6% in the United States. In patients with chronic GERD, the frequency of BE is higher with a prevalence of 3.6%-10.3% in Western literature<sup>(5)</sup>. Asian studies represent lower prevalence of BE<sup>(6)</sup>. The male / female ratio is approximately 2/1. Barrett's esophagus is 6-10 times more likely in patients with chronic heartburn than those without. Best-defined risk factors for Barrett's esophagus; being older than 50 years, male gender, white race, chronic GERD, hiatus hernia, increased body-mass index, metabolic syndrome and intra-abdominal distribution of body fat, increased insulin resistance, increased serum leptin and low adiponectin levels<sup>(5)</sup>. The presence of columnar mucosa in the distal esophagus is not always a condition that causes

symptoms alone. Symptoms in these patients are often associated with prolonged GERD (e.g., esophagitis, peptic adhesions, etc.). The absence of symptoms of chronic reflux does not exclude the possibility of BE.

Barrett's esophagus is classified as short-segment Barrett's esophagus (SSBE) and long-segment Barrett's esophagus (LSBE) according to the length of the metaplastic epithelium on endoscopy. If the length of the columnar-like mucosa is as far as 3 cm above the proximal margin of the gastric folds, it defines LSBE. If the length of the columnar-like mucosa is less than 3 cm, it is also named as SSBE<sup>(7)</sup>. As a newer classification model, Prague classification, the evaluation is made by measuring the circumference (C) and the maximum length (M) on the gastroesophageal junction according to the endoscopic appearance<sup>(8)</sup>.

Barrett's esophagus is a premalignant condition; dysplasia is usually the step before the development of adenocarcinoma. Especially white men with chronic reflux have a high risk. Medical or surgical reduction of reflux reduces the progression or occurrence of the disease<sup>(4)</sup>. Various treatments are being developed for the reversal of Barrett's esophagus and the reduction of cancer risk, which are medical treatment of acid reflux, anti-reflux surgery and endoscopic treatments. Current treatments include combinations of endoscopic mucosal resection techniques to eliminate lesions that can be seen following residual metaplastic tissue ablation. In multifocal high grade neoplasia or mucosal Barrett's carcinoma that cannot be treated with an endoscopic approach, esophagectomy is still the current method of choice<sup>(9)</sup>.

The aim of this study is to evaluate the demographic, clinical, endoscopic and pathological findings of patients diagnosed with BE by histopathological evaluation on biopsies taken on the appearance of compatible with Barrett's esophagus on esophagogastroduodenoscopy (EGD) and to determine the frequency of *Helicobacter pylori* (*H. pylori*) in patients with BE in a center at Eastern Turkey.

## Methods

In this study, patients with an appearance compatible with BE in EGD were included. The medical records of patients undergoing EGD for any indication at the Firat University Medical Faculty Hospital between January 2015 and December

2017 were retrospectively reviewed. All EGDs were performed using Olympus GIF-170 (Olympus, Tokyo, Japan) video-endoscopes. The patients who had endoscopic findings compatible with Barrett's esophagus were recorded. The demographic characteristics, EGD indications, and endoscopic findings of patients who were diagnosed as BE were noted. Other recorded endoscopic findings were as follows: presence of lower esophageal sphincter (LES) dysfunction or hiatus hernia (HH), erosive esophagitis, and the presence and type of gastritis.

Endoscopic BE was diagnosed as the extension of salmon-colored mucosa into the esophagus, beyond 1 cm proximal to esophagogastric junction (EGJ). Presence of EGJ irregularity, presence of salmon-colored mucosa as islet/nodular shaped or proximal extension of salmon-colored mucosa less than 1 cm were not considered as BE and excluded from final analysis. Patients were subdivided into SSBE or LSBE depending on the endoscopists' estimation of columnar-mucosal extension length (less than or more than 3 cm).

The pathology specimens of patients who were considered to have BE endoscopically and who were diagnosed as BE as a result of the examination of biopsy specimens, re-evaluated and confirmed by the study pathologist (GA). The diagnosis of histopathological Barrett's esophagus based on the presence of columnar metaplasia with or without the presence of goblet cells. The presence and degree of dysplasia (low grade dysplasia or high degree dysplasia) were noted. The presence of *H. pylori* and intestinal metaplasia at gastric biopsy specimens was also recorded.

Statistical analyses were performed using SPSS (version 21; SPSS Inc., Chicago, Illinois, USA). Categorical variables were displayed as numbers and percentages. Continuous variables were represented as mean  $\pm$  standard deviation (minimum-maximum). Categorical variables were compared using the  $\chi^2$  test or Fischer's exact test. Differences between continuous variables were analyzed using Student's t-test.  $P < 0.05$  was considered statistically significant. Approval was obtained from Firat University Faculty of Medicine Non-Interventional Ethics Committee on 20.12.2018 with the decision numbered 21/07.

## Results

A total of 8275 reports of patients undergoing EGD between January 2015 and December 2017 were screened retrospectively. Patients

who were reported as endoscopic BE but whose histopathological sampling was not performed from EGJ were excluded from the study. A total of 241 (2.9%) patients who had endoscopic appearance consistent with BE and histopathologic examination for BE were recruited. Pathology specimens were re-evaluated by study pathologist. Endoscopic BE was recorded as islet or nodular shaped in 49 patients, so they were excluded. Thirty-one patients had no histopathological finding consistent with BE. One hundred sixty-one specimens were consistent with BE and they underwent the final analysis. Histopathological BE was detected in 1.9 % of all upper endoscopies.

Among the patients with BE, 82 (51%) were women. The mean age was  $48.0 \pm 16.7$  years (19 years - 95 years, minimum-maximum) and, 74 of them (46%) were over 50 years. Endoscopy was performed for typical reflux symptoms (regurgitation or heartburn) in 37 patients (23%), dyspepsia and epigastric pain in 79 patients (49%). Remaining patients underwent EGD for other indications.

On endoscopic examination, lower esophageal sphincter (LES) was evaluated as normal in 62 subjects (39%). LES dysfunction was also evident in 57 subjects (35%) and, HH in 42 subjects (26%). Esophagitis was detected in 30 (19%) subjects. Twenty-seven of patients with HH (73 %) and 15 of patients without HH (12%) underwent EGD for reflux-related symptoms ( $p < 0.01$ ). Similarly, reflux-related symptoms were indications for EGD in 14 patients with esophagitis (38 %) and 16 patients without esophagitis (13%) ( $p < 0.01$ ). Moreover, HH was detected in 53% of patients with esophagitis, 20% of patients without esophagitis ( $p < 0.01$ ).

Endoscopic Barrett's esophagus was found as SSBE in 153 subjects (95%) and as LSBE only in 8 subjects (5%). Hiatus hernia was detected in six patients with LSBE, other two had LES dysfunction. Half of them underwent EGD for reflux related symptoms. Six of them were men and six of them were over 50 years. Dysplasia was detected in 2 of patients with LSBE (25%), and 5 of patients with SSBE (3.3%) ( $p = 0.04$ ). Gastric endoscopic findings were: pancreatitis in 79 (49%), antral gastritis in 38 (23.5%), erosive gastritis in 38 (23.5%) and other types of gastritis in 6 (4%).

Histopathological examination revealed the presence of columnar metaplasia without dysplasia in 154 (96%), and low grade dysplasia in 7 (4%). No high-grade dysplasia or carcinoma was found. Six of them were over 50 years (between 57 years – 74

years), one was under 50 years (8.1% vs 1.1%,  $p = 0.04$ ). *Helicobacter pylori* colonization was detected in gastric biopsy samples of 111 patients (61%). Gastric intestinal metaplasia was found in 22 (14%).

	Female (n=88), n(%)	Male (n=84), n(%)	p
Age, years	$45.1 \pm 16.3$	$51.1 \pm 16.7$	<b>0.02</b>
Age > 50 years	36 (41)	44 (53)	0.13
Indications			<b>0.03</b>
Reflux symptoms	14 (16)	27 (32)	
Dyspepsia / epigastric pain	51 (58)	35 (42)	
Other indications	23 (26)	22 (26)	
Dysphagia	3 (3.4)	1 (1.2)	
Diarrhea / malabsorption	3 (3.4)	2 (2.4)	
Refractory vomiting	0 (0)	2 (2.4)	
Anemia	9 (10.2)	5 (5.9)	
GI bleeding	1 (1.1)	4 (4.8)	
Portal hypertension	1 (1.1)	2 (2.4)	
Malignancy screening / weight loss	2 (2.2)	4 (4.8)	
Previous gastric surgery	2 (2.2)	2 (2.4)	
Other	2 (2.2)	0 (0)	

**Table 1:** Demographical and clinical data of patients of Barrett's esophagus in terms of gender.

	Female (n=88), n(%)	Male (n=84), n(%)	p
<b>Endoscopic findings</b>			
<b>LES findings</b>			
Normal LES	37	27	0.18
LES relaxation	35	29	
Hiatus hernia	16	28	
Presence of hiatus hernia	16	28	<b>0.02</b>
Esophagitis	14	18	0.43
Barrett's esophagus			0.16
Short Segment BE	86	78	
Long Segment BE	2	6	
<b>Gastritis type</b>			0.33
Antral gastritis	22	18	
Pangastritis	40	46	
Erosive gastritis	23	17	
Alkaline reflux gastritis	0	2	
Atrophic gastritis	3	1	
<b>Histopathological findings</b>			
<b>Presence of BE</b>			0.27
No dysplasia	86	79	
Low grade dysplasia	2	5	
High grade dysplasia	-	-	
<b>H. pylori colonisation</b>	62 (70)	60 (71)	0.89

**Table 2:** Endoscopic and histopathological findings of patients of Barrett's esophagus in terms of gender.

We compared the patients with BE in terms of gender. Female patients with BE were younger than male patients ( $45.1 \pm 16.3$  vs.  $51.1 \pm 16.7$ ,  $p = 0.02$ ). While dyspepsia and epigastric pain were more prevalent among females, typical reflux symptoms (heartburn and/or regurgitation) were less than male patients with BE. Table 1 summarizes demographical data of female and male subjects. On endoscopic examination, hiatus hernia was found in 27 of male patients (34%) and 15 female patients (18%) ( $p = 0.02$ ). In concordance with hiatus hernia, esophagitis was detected in 18 of males (23%) and 12 females (15%) ( $p = 0.18$ ). LSBE was found in 2 of female patients (2.4%) and in 6 of male patients (7.6%) ( $p = 0.16$ ). On histopathological examination, low grade dysplasia was evident in 2 female (2.4%) and 5 male subject (6.3 %) ( $p = 0.27$ ). *Helicobacter*

pylori colonization was detected in 56 (68%) of females and in 55 (70%) of males ( $p=0.86$ ). Gastric intestinal metaplasia was found in 7 (9%) of females and in 15 (19%) of males ( $p=0.06$ ). Endoscopic and histological findings of patients in terms of gender were given in Table 2.

## Discussion

The definition of BE varies worldwide. While the presence of endoscopically visible columnar metaplasia is considered to be sufficient for the diagnosis of BE in some countries like England, goblet cells (intestinal metaplasia) are required for diagnosis in countries such as the USA<sup>(10, 11)</sup>. We used the presence of columnar metaplasia in the distal esophagus with a minimum length of 1 cm for the definition of BE in this study.

The prevalence of BE in the general population is not known and most of the studies determine the prevalence of BE among patients undergoing endoscopy for any clinical indication. Data about the prevalence and endoscopic appearance of BE has also inconsistent results worldwide. A recent meta-analysis demonstrated a pooled prevalence of BE in general population as 2.30% in Western countries and 0.59% in Eastern countries<sup>(12)</sup>. The pooled prevalence of BE among GERD patients was 9.30% in Western countries and 4.73% in Eastern countries according to the same meta-analysis. In another recent metaanalysis, the overall prevalence of histologically confirmed BE in individuals with GERD was estimated as 7.2%, with a lower reported prevalence of BE as 0.6% from Turkey<sup>(13)</sup>. In Eastern countries, the prevalence of BE appears to be lower when compared to Western countries. Moreover, while LSBE is more common in Western countries, SSBE is more common in Eastern countries<sup>(14)</sup>. Turkey has a unique pattern of GERD, with a higher prevalence of GERD in the general population like Western countries and, a regurgitation dominant profile like Eastern countries<sup>(15)</sup>. The results of previous studies from Turkey showed that the prevalence of BE seems to be much lower than that of western countries and SSBE is more prevalent than LSBE in Turkish population like Asian countries<sup>(16)</sup>.

In the present study, we found the prevalence of histopathological BE as 1.9% among subjects undergoing EGD for any clinical indications. In previous studies from Turkey, BE prevalence was investigated among populations living in Western and Central Anatolia. On the other hand, there is

no study investigating BE prevalence from Eastern part of Turkey. In a retrospective study from Western Turkey, the prevalence of BE was found as 1.5% endoscopically and 0.4% histologically among 18766 subjects undergoing EGD in a five years period<sup>(16)</sup>. BE was found as 2% and erosive esophagitis as 17% in a prospective study from Western Anatolia among 645 patients with GERD<sup>(17)</sup>. Odemis et al. found histologically proven BE prevalence among 1000 consecutive patients undergoing EGD for any reasons as 1.2% in Central Anatolia<sup>(18)</sup>. Multicenter GORHEN study from Turkey also demonstrated a prevalence of endoscopic BE as 4.3% and histopathological BE as 1.3% among 1421 patients with GERD in multicenter GORHEN study<sup>(19)</sup>. We performed a literature search and found few studies from Turkey, with most of them from Western and Central Anatolia. To the best of our knowledge the present study is the first study examining BE prevalence in a large cohort of patients undergoing EGD from Eastern Anatolia. When compared to the studies from other regions of Turkey, BE prevalence was found higher in our study. Our result resembles the BE prevalence of unselected populations in Western countries. It may be associated with the differences in ethnicity and genetic background or, may be related to nutritional habits.

Several risk factors have been linked to an increased risk of BE including older age, male gender, chronic GERD, smoking, central obesity and reduced *H. pylori*<sup>(5)</sup>. Our results showed that among patients who underwent EGD for any reason in a 2-year period, the number of men and women who was detected BE was equal. Approximately one half of patients was under 50 years old. In the comparison of patients in terms of gender, we found that BE was diagnosed in younger ages among females compared to males. In the literature, BE is defined as a male predominant disorder. Studies revealed that the prevalence of BE in females began to increase after 60 years of age<sup>(20)</sup>. Male predominance and delay in women has been linked to hormonal changes. Probably, different risk factors for BE might be responsible for such different prevalence rates in our population. While reflux related symptoms were seen predominantly in female patients, dyspepsia and epigastric pain are more prevalent indications for EGD in males. This result is consistent with a previous study from Turkey<sup>(21)</sup>. On the other hand, LSBE was more prevalent in male patients in accordance with literature<sup>(20)</sup>. *Helicobacter pylori* prevalence was similar between females and males.

Bor et al. was found similar *H. pylori* prevalence rates in a previous study from Turkey<sup>(22)</sup>.

There are several limitations of the present study. The study was retrospective in nature, and therefore it has the limitations of such retrospective study designs. It is possible that BE could have been under-recognized due to the absence of biopsy samples of suspected areas of BE or insufficient sampling. Therefore, we included in the study those who met the both endoscopic and histopathological criteria, not only endoscopic criteria for BE. Due to the lack of sufficient documentation, possible risk factors of BE such as BMI, obesity, smoking and alcohol habits could not be evaluated.

In conclusion, we found a higher prevalence of BE in one tertiary center from Eastern Turkey when compared to other parts of Turkey. Similar prevalence rates of BE in female and male subjects and the presence of BE in younger ages for especially female subjects were interesting results of this study. Our results should be further investigated in larger cohorts in the Eastern part of Turkey prospectively.

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*Corresponding Author:*

ABDURRAHMAN SAHIN

Universite Mah.Yunus Emre Bulv. No:20, 23200, Elazig

Email: asahin@firat.edu.tr

(Turkey)