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Prevalence and risk factors for Barrett's esophagus in patients with chronic gastroesophageal reflux disease

Преваленца и фактори ризика за настанак Баретовог једњака код болесника са хроничном гастроезофагеалном рефлуксном болести

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Преваленца и фактори ризика за настанак Баретовог једњака код болесника са хроничном гастроезофагеалном рефлуксном болести

SUMMARY

Introduction/Objective The most important complication of gastroesophageal reflux disease (GERD) is Barrett's esophagus (BE) and the development of esophageal adenocarcinoma. Prevalence of BE is from 5 to 15% in patients with symptoms of GERD. The aim of the study was to investigate the prevalence and risk factors for BE in patients with chronic reflux symptoms. A prospective study was conducted in the Clinic of Gastroenterology, Clinical Center Nis.

Methods We included 676 patients with chronic reflux symptoms, who underwent esophagogastroduodenoscopy. The biopsy specimens were obtained in a four-quadrant fashion at intervals of 2 cm from the circumferential endoscopic Barrett's epithelium in the distal esophagus. BE was diagnosed by pathological examination.

Results Out of total number patients with GERB, 92 of them were diagnosed with columnar-lined esophagus (CLE), the prevalence being 13,60%. After histological examination of biopsy from 92 patients with CLE revealed specialized intestinal metaplasia (SIM) in 15 patients with the prevalence of 2.22%. Compared to patients without BE, patients with BE were older and more commonly men. Univariable analyses showed that hiatal hernia (HH) and Helicobacter pylori infection were two significant risk factors for the onset of esophagitis. The age and the presence of reflux symptoms were associated with the presence of BE. Older age could be considered a significant risk factor for the development of BE and GERD.

Conclusion Prevalence of biopsy proven BE and CLE in Serbia was 2.22% and 13.60%, in patients with symptoms of GERD.

Keywords: Barrett's esophagus, gastroesophageal reflux disease, chronic reflux symptoms

САЖЕТАК

Увод/Циљ Најважнија компликација гастроезофагеалне рефлуксне болести (ГЕРБ) је појава Баретовог једњака (БЈ) и настанак аденокарцинома. Преваленца БЈ је од 5 до 15% код пацијената са симптомима ГЕРБ-а. Циљ ове студије био је испитивање преваленце и ризичних фактора за настанак БЕ код пацијената са хроничним симптомима рефлукса. Истраживање је спроведено у Клиници за гастроентерологију Клиничког центра у Нишу.

Методе Укључено је 676 болесника са хроничним рефлуксним симптомима, којима је урађена езофагогастродуоденоскопија. Биопсије су узимане из 4 квадранта у дисталном делу једњака, на удаљености од 2цм од ендоскопски суспектног БЈ. БЈ је дијагностикован патолошким прегледом.

Резултати Од укупног броја пацијената са ГЕРБ-ом, суспектан БЈ је нађен код 92 пацијента, што чини преваленцу од 13,60% у нашој студији. Након хистолошког испитивања биопсије суспектог БЈ, нађена је специјализована интестинална метаплазија (СИМ) у 15 пацијената, са преваленцом од 2.22%. У поређењу са пацијентима без БЈ, пацијенти са БЈ су старији, чешће мушкарци, у оба параметра са статистичким значајношћу. Хијатална хернија и Хеликобактер пилори инфекција су два значајна фактора ризика за настанак езофагитиса. Старост и присуство симптома рефлукса су повезани са присуством БЈ. Старији узраст може представљати значајан фактор ризика за развој БЈ и ГЕРБ-а.

Закључак Преваленца хистолошки доказан БЈ и суспектог БЈ у Србији је била 2,22% и 13,60%, код пацијената са симптомима ГЕРБ-а.

Кључне речи Баретов једњак, гастроезофагеална рефлуксна болест, хронични рефлуксни симптоми

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a long-term condition where stomach contents come back up into the esophagus resulting in either symptoms or complications. GERD is mild acid reflux that occurs at least twice a month, or moderate to severe acid reflux that occurs at least once a week. In 20% of the population, symptoms last longer than one week. The prevalence of GERD

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significantly varies among different populations. The prevalence of all forms of GERD is 40%, the weekly symptoms have 14% of the population, and the daily symptoms range from 4-7% [1]. Peptic esophagitis, reflux esophagitis and erosive esophagitis, erosive reflux disease (ERD) are synonyms for the subgroup of patients with GERD with histopathological changes of esophageal mucosa that usually correlate with the symptoms of acid reflux content. Non erosive reflux disease-NERD includes a group of patients with symptomatic GERD who have no macroscopic mucosal changes noticed on the esophagogastroduodenoscopy. It is estimated that 50-70% of patients with GERD have NERD. Symptoms and signs of esophageal reflux disease can be varying intensity and are not always in correlation with the severity of esophageal damage [2].

BE is a consequence of chronic GERD, that predisposes the development of esophageal adenocarcinoma (EAC) [3]. Endoscopically, the prevalence of BE has been estimated at 1-2% in all patients underwent upper endoscopy for any indication, and anywhere from 5 to 15% in patients with symptoms of GERD. Among the malignant tumors of the esophagus, the incidence of Barrett's adenocarcinoma is increasing. The incidence of EAC has been 3-4 times higher in the last two decades. It is believed that the main reason for this high percentage of Barrett's adenocarcinoma is related to an increased incidence of BE, that shows a close causal relationship with GERD [4]. However, not all patients with gastroesophageal reflux and erosive esophagitis will develop BE and all patients with BE do not have a history of gastroesophageal reflux. At least, 25% of patients with BE do not have history of GERD. In many patients with reflux esophagitis, treatment leads to regeneration of the mucosa. Some patients will develop BE with an increased risk of developing EAC. There are many risk factors that can contribute to the development of BE, which is the subject of many studies in the world [5,6].

The esophagus lined with columnar epithelium (CLE) and BE are the conditions in which stratified squamous epithelium is continuously replaced by a cylindrical epithelium from an esophagealgastric junction. BE is characterized by the presence of specialized intestinal metaplasia (SIM). As SIM is part of the definition and is the epithelial type associated with cancer, obtaining biopsies from the columnar lined distal esophagus is mandatory. The sensitivity and positive predictive values of standard upper endoscopy for diagnosing BE have been reported as 82% and 34%, respectively [7]. Guidelines of the American College of Gastroenterology state that every patient with gastroesophageal reflux symptoms should at least once in a lifetime be referred for BE screening endoscopy. Patients with SIM in CLE are currently advised to undergo a periodic endoscopic surveillance to detect progression to dysplasia at an early, potentially curable stage. New techniques such as chromoendoscopy and magnification endoscopy have been tried to improve recognition of SIM [4].

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The aim of this study was to determine the prevalence and possible risk factors of BE in patients with chronic reflux symptoms.

METHODS

A prospective study conducted in the Clinic of Gastroenterology, Clinical Center in Nis, included 676 patients with chronic reflux symptoms and all underwent esophagogastroduodenoscopy. Symptoms are defined as the presence of heartburn and regurgitation at least three times a week for one year. A questionnaire was completed by every patients, including age, sex, occupation and also including the following criteria: primary referral symptoms, frequency of GERD symptoms, acid test, extra esophageal symptoms. Patients with history of documented peptic disease, gastric or esophageal surgery and those with motor disorders such as achalasia, diffuse esophageal spasm, or scleroderma were excluded. Gastroesophageal junction (GEJ) is defined as the beginning of the proximal limit of gastric mucosal folds (figure 1). CLE was identified as a columnar epithelium over 1 cm from the GEJ which had a reddish color and a velvety texture that could be easily distinguished from the normal pale and glossy esophageal squamous epithelium. The length of the CLE was estimated by subtracting the distance from the incisors to the squamocolumnar junction (Z-line) from the distance from the incisors to the GEJ (figure 2). Patients were classified to short-segment BE (SSBE) if the length of the columnar appearing mucosa was less than 3 cm above the GEJ and long segment BE (LSBE) if the length of the columnar mucosa was equal to or greater than 3 cm. Diagnosis BE is based on the presence of endoscopic findings compatible with columnar epithelium in the distal esophagus and confirmed by the presence of SIM on biopsies (figure 3).

The study protocol was approved by the local ethics committee and all patients gave their informed consent to be included. All patients were fully informed of the study protocol and agreed to undergo upper GI endoscopy.

All upper endoscopies were performed using a GIF100 or GIF130 video endoscope (Olympus, Lake Success, NY). Macroscopic mucosal changes of the distal esophagus were measured on the basis of the distance from the Z line, and mucosal damage was classified according to the Los Angeles classification of reflux esophagitis [8].

The presence of a hiatal hernia and its size was determined in all patients, during withdrawal of the endoscope and was measured in centimeters. We investigated the presence of Helicobacter pylori infection in all patients by using pathology and rapid urease test-RUT.

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The biopsy specimens were obtained in a four-quadrant fashion at intervals of 2 cm from the circumferential endoscopic Barrett's epithelium in the distal esophagus. In patients with small islands or irregular tongues of columnar appearing mucosa, at least two specimens were obtained within the abnormal-appearing mucosa at intervals of 1cm from the GEJ to the proximal extent of the abnormality. All biopsy specimens were stained with hematoxylin and eosin (H&E) and with alcian blue (pH 2.5) stain.

Statistical analysis

The processing of the obtained data was made using the statistical software package -Statistical Package for Social Science (SPSS) software, version 11.0 in the Windows environment, with the results shown in the tables and graphs. Data were processed using standard descriptive statistical methods (mean value, standard deviation and percentage representation). The results were analyzed using the appropriate tests depending on the size of the group, type of mark and type of distribution. We used the Student'st test for continuous variables and χ2test for categorical variables, in comparative analyses. A univariate analysis was performed to determine the variabkles independently associated with the risk of BE. A p valule <0.05 was considered statistically significant.

RESULTS

Patient with GERD: The average age of subjects with symptoms of reflux disease was 50±13 years. There were 381 men (56.36%) and 295 women (43.64%). Based on endoscopic findings, patients were divided into two groups: NERD group included 403 (59.61%) patients and ERD group included 273 patients (40.39%). Of patients in ERD group, esophagitis A grade was found in 64.44%, B grade in 26.66%, and C grade in 8.88%. Esophagitis D grade was not found in any respondent. The mean age of patients in both groups did not differ significantly (p=0.07). The percentage of respondents by sex was approximately the same. Of the clinical manifestations of reflux disease, the heartburn symptom significantly correlates with ERD (p=0.013). Heartburn was equally represented in groups compared to the day time. In both groups of patients was more frequent heartburn at day (ERD, p=0.00001; NERD, p=0.00001), while fewer patients in both groups had heartburn at night. The symptom of regurgitation was more frequent in the NERD group in 222 (55.08%), but without statistical significance. Hiatal hernia was more frequent in the ERD group, with a statistically significant (p=0.001). H. pylori infection was significantly higher in NERD patients, 24.81% (n=100). There was no correlation between the presence of H. pylori infection and the existence of reflux symptoms (Table1).

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Prevalence of CLE: Of all patients with GERD, 92 patients had CLE, with the prevalence of 13.60% of all patients with GERD. Sixty-five patients were found to have normal endoscopy and 27 had erosive esohagitis ($\chi 2=27.39$; $p=0.001$). On endoscopic examination of all 92 patients, 35% had circumferential CLE, 34% had tongue like extensions and 31% isolated islands. A short CLE segment was found in 56% of patients and a long CLE segment was found in 13% of patients.

Prevalence of BE: After histological examination of biopsy from 92 patients with CLE revealed SIM in 15 patients, with the prevalence of 2.22% in our study. Of the 15 patients with BE, nine patients were found to have a long BE segment and 6 had a short BE segment. Patients with BE were the average age of 59±15 years and 12 of them (80%) were male. The percentage of patients with CLE who had a SIM was 16.30%, and were more frequent with a long CLE segment. The largest number of patients did not have erosive changes in the esophagus during endoscopy (87%), and the hiatal hernia was noticed in 80% of patients with BE (Table2).

Prevalence of BE in GERD: Compared to patients without BE, patients with BE were older and more commonly men, with statistical significance ($p=0.001$). The symptom of heartburn was the dominant symptom, statistically occurring more frequently in a patient with BE ($p=0.04$). In the univariate analyses showed that hiatal hernia and H. pylori infection were two significantly risk factors for the onset of esophagitis. The age and the presence of reflux symptoms are associated with the presence of BE (Table3).

DISCUSSION

In the last decades, the lower part of the esophagus and cardia have been in the focus of extensive research. The reason for this is a dramatic increase in the incidence of adenocarcinoma of the esophagogastric junction. In comparison, the incidence of GERD and BE as one of its complications was also noticed. Some data indicate a 10-fold increase in the incidence of Barrett's esophagus in Western European countries in the last few decades. Barrett's metaplasia is considered an intermediary event in the development of EAC [9].

In our study, the average age of subjects with symptoms of reflux disease was 50±13. Almost 60% of patients with GERD did not have endoscopic signs of esophagitis, which is similar to those of Western countries that show that 60-70% of patients with typical reflux symptoms do not have damage of esophageal mucosa during endoscopy. In both groups, men were more than women, without statistical significance. Male gender has been reported to be an independent risk factor for esophagitis. Different parietal cell mass, lower esophageal function or body mass index between

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genders have been proposed as possible causes to explain the gender effect. [10]. Sharma et al show the prevalence of male sex in a patient with GERD [11].

Of the clinical manifestations of GERD, the heartburn symptom was statistically more frequent in the ERD group compared to the NERD group (p=0.013), but there was no statistically significant association of heartburn symptoms with the degree of esophagitis. GERD symptoms have been inconsistently correlated with endoscopic findings of EE in different studies, some of which favor such correlation, though not with all reflux symptoms and some argue against it [12].

Hiatal hernia is present in 37.13% of patients with GERD. In the ERD group, the hiatal hernia is present in 58.61% of the patients. We found that the presence of hiatal hernia is a strong risk factor for esophagitis (p=0,001) [13].

The relationship between H. pylori and GERD infection is relatively unclear. H. pylori gastritis can lead to acid hyposecretion and loss of symptoms of burning sensation [14]. In our study, H. pylori infection was statistically more common in the NERD group than in the ERD group (p=0.04). We did not find a statistically significant relationship between the presence of H. pylori infection and the presence of typical reflux symptoms.

Of all patients with GERD, the suspected CLE was found in 92% of patients, representing prevalence of 13.60% of patients with GERD. Sixty-five patients were in the NERD group, and 27 in the ERD group. (χ^2=27.39; p=0.001). Of the 92 patients with suspected CLE revealed SIM in 15 patients, with the prevalence of 2.22% in our study. The prevalence of BE worldwide is different, it is assumed to be higher in the western than in the eastern countries of the world. Westhoff et al showed a prevalence of 13.2% [15]. Ronkainen et al showed a prevalence of 2.3% in Sweden [16], while Kim et al show a prevalence of less than 1% in Korea [17]. In our study, BE was more common in men (80%) than patients without BE (56.02%). BE prevalence was statistically more common in men than in women (p<0.05). Li et al in their study showed that 14% of women had BE compared to 23% of men with BE (p<0.05) [18]. Male sex has been reported to be risk for BE. Age has been also considered a risk factor for BE. Edelstein et al. noted that risk of BE increased with increased age [19]. In our study, patients with BE was significantly older then in those without BE (p=0.001). In a clinical manifestation, we found a significant difference between patients with BE and those without BE for heartburn, which more evident in patients with BE. The symptoms of reflux in our study was a good predictor of the risk for BE (p=0.04), which is in a line with another study. Hak et al in their study show that the duration of reflux symptoms is longer in patients with BE than those without BE [20]. In our study, we noticed a significant difference in the existence of hiatal hernia between groups, hiatus hernia was more common in patients with BE. Herrera et al in their study show that hiatus hernia is independently associated with the presence of BE [21].

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In our study, we did not find that EE is a predictor for the appearance of BE. Different morphological types of BE are not a risk factor for BE. The CLE length is a risk factor for BE. The CLE length was 3 cm in a patient with BE compared to 1.8 cm in a patient without BE (p=0.001). Okita et al in their study also prove that the long segment of the BE is a predictor of SIM in the histological examination [22, 23,24,25]. In our study, we did not show the presence of dysplasia in any of the patients with BE.

In conclusion, the prevalence of endoscopic suspecting CLE in GERD patients is 13.60%. The prevalence of histologically proven BE was 2.22% in the patient with GERD in our area. The presence of hiatal hernia, reflux symptoms and long segment of CLE are independently associated with the presence of BE. Older age could be considered a significant risk factor for the development of BE and GERD.

CONCLUSION

A large number of studies have noted that most patients who have endoscopically suspected BE did not have SIM on histological samples. Multicentre studies are required for more clearing determining the epidemiology of BE, after which a cost-effective strategy for BE screening and surveillance can be developed. Studies should be carried out to determine endoscopic predictors, which can be used as surrogate markers for the histological BE, and that only patients with this predecessor are subjected to biopsy.

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Table 1. Background characteristics of the study groups

Characteristics	**NERD (n = 403)**	**ERD (n = 273)**	**p-value**
Age	49±15	52±17	0.07
Sex			
Male	220 (54.59%)	161 (58.97%)	0.30
Female	183 (45.41%)	112 (41.03%)	
Hiatal hernia			
Yes	91 (22.58%)	160 (58.61%)	0.001
No	312 (77.42%)	113 (41.39%)	
RUT			
Yes	100 (24.81%)	86 (31.50%)	0.05
No	303 (75.19%)	187 (68.50%)	
Heartburn	239 (59.30%)	190 (69.58%)	0.013
Regurgitation	222 (55.09%)	158 (57.87%)	0.54

RUT – rapid urease test

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Table 2. Predictors of SIM or Barrett s esophagus

Characteristics	**No metaplasia (n = 77)**	**Metaplasia (n = 15)**	**p-value**
Age	49±12	59±15	0.001
Male	59 (76.62%)	12 (80%)	0.61
Female	18 (23.38%)	3 (20%)	0.58
Heartburn	53 (68.83%)	2 (13.33%)	0.004
Regurgitation	19 (24.68%)	10 (66.67%)	0.12
NERD	52 (67.53%)	13 (86.67%)	0.34
ERD	25 (32.47%)	2 (13.34%)	0.25
Hiatal hernia	40 (51.95%)	12 (80%)	0.17
CLE			
Short segment	47 (61.04%)	6 (33.34%)	0.29
Long sengment	3 (3.89%)	9 (53.34%)	0.005

NERD – non erosive reflux disease; ERD – erosive reflux disease; CLE – the esophagus lined with columnar epithelium

Paper accepted

Table 3. Background characteristics of the study groups

Characteristics	**BE** **(n = 15)**	**Without BE** **(n = 661)**	**p-value**
Age	59±15	49±15	0.001
Male Female	12 (80%) 3 (20%)	372 (56.28%) 289 (43.72%)	0.06
Heartburn	2 (13.33%)	414 (62.63%)	0.04
Hiatal hernia Yes No	 12 (80%) 3 (20%)	 244 (36.91%) 417 (63.09%)	 <0.05
RUT Yes No	 4 (26.66%) 11 (73.34%)	 182 (27.53%) 479 (73.47%)	 0.43

RUT – rapid urease test

Paper accepted

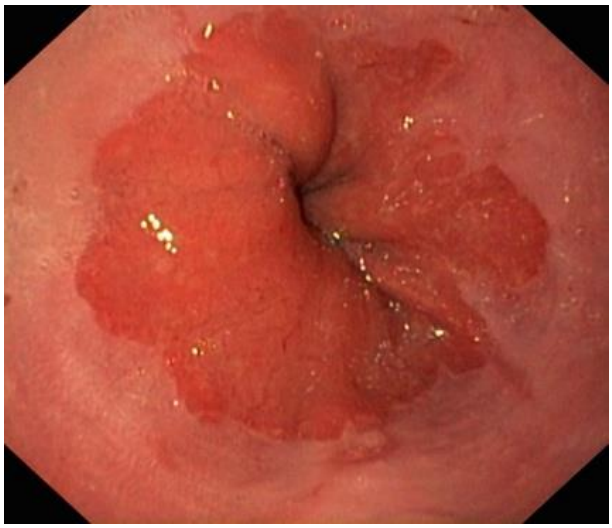

Figure 1. Endoscopic appearance of normal gastroesophagel junction; note that the squamocolumnar line corresponds with proximal extent of the gastric folds

Paper accepted

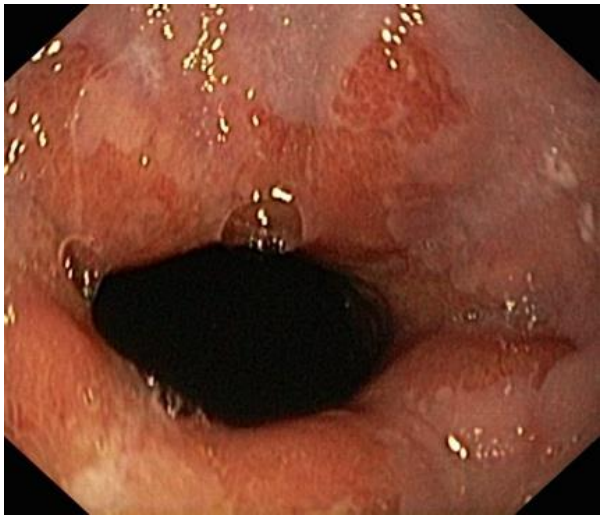

Figure 2. Salmon-colored mucosa is seen extending proximal to the gastroesophagel junction consistent with Barrets esophagus

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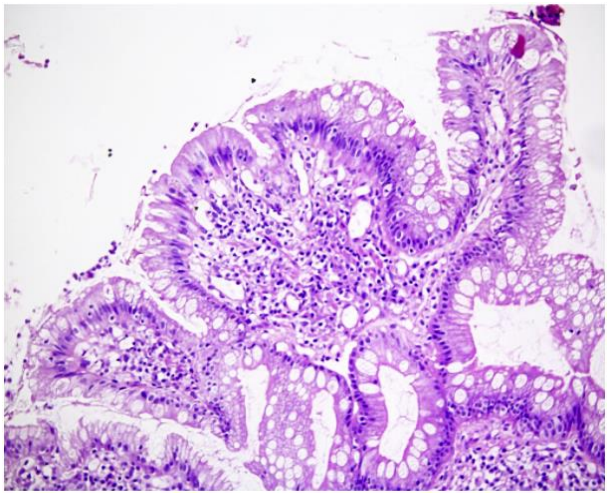

Figure 3. Histological appearance of Barrett epithelium; intestinalized mucosa with branching pits and goblet cells (H&E, obj.×20)

Paper accepted