Risk Factors for Erosive Esophagitis and Barrett's Esophagus in a High *Helicobacter pylori* Prevalence Area

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Key words: *erosive esophagitis; Barrett's esophagus; Helicobacter pylori; prevalence.*

Summary. *Objective. To establish the prevalence and risk factors of erosive esophagitis (EE) and Barrett's esophagus (BE) among patients routinely referred for upper endoscopy.*

Material and Methods. A total of 4032 consecutive patients referred to a regional hospital for upper endoscopy due to upper gastrointestinal and/or "alarm" symptoms were examined. Analysis was performed on the prospectively selected patients (40 in each group) with EE of different grades and BE.

Results. EE was diagnosed in 474 patients (11.75%): grade A, in 194 (41%); grade B, in 167 (35%); grade C, in 65 (14%); and grade D, in 48 patients (10%). Increasing severity of erosive esophagitis and presence of its complication – Barrett's esophagus – were associated with the decreasing prevalence of H. pylori and increasing hiatal hernia size (P<0.05). Male gender (OR, 3.57; 95% CI, 1.12 to 10.62), hiatal hernia >2 cm (OR, 3.73; 95% CI, 1.60 to 8.68), and absence of H. pylori (OR, 4.24; 95% CI, 1.07 to 16.84) were the factors found to be associated with severe EE. The factors associated with BE were as follows: ulcer and/or stricture of esophagus (OR, 11.94; 95% CI, 2.51 to 41.37), age >60 years (OR, 1.06; 95% CI, 1.01 to 1.20), smoking >10 cigarettes per day (OR, 4.62; 95% CI, 1.01 to 12.50), hiatal hernia >2 cm (OR, 5.22; 95% CI, 1.86 to 14.64), and absence of H. pylori (OR, 5.60; 95% CI, 1.38 to 22.72).

Conclusions. The prevalence of EE was found to be low, and the prevalence of BE was found to be very low among routinely endoscoped patients in primary and secondary care settings in a Lithuanian rural area with high H. pylori prevalence. Increasing severity of gastroesophageal reflux disease was associated with the decreasing prevalence of Helicobacter pylori.

Introduction

The incidence and prevalence of gastroesophageal reflux disease (GERD) are increasing in well-developed European and North American countries (1). An increase in the incidence of precancerous Barrett's esophagus and esophageal adenocarcinoma has become one of the major health concerns over the last decade (2). The incidence of the latter malignant disease continues to increase greater than the incidence of any other common epithelial malignancy (3, 4). The prevalence of erosive esophagitis and Barrett's esophagus varies across the world. The majority of epidemiological data are coming from economically well-developed regions, where the prevalence of GERD and Barrett's esophagus is high whereas the prevalence of *Helicobacter pylori* (*H. pylori*) infection in population is low. Different factors possibly promoting the development of erosive esophagitis and Barrett's esophagus have been described, but the exact identification of population at risk is still not possible (5, 6). The prevalence of erosive esophagitis and Barrett's esophagus is not known in Eastern and Central Europe, including Lithuania where the prevalence of *H. pylori* infection in population is high (7, 8). Many questions related to epidemiology, risk factors, and prevention of erosive esophagitis and Barrett's esophagus remain unanswered. Therefore, the aim of our study was to determine the prevalence of erosive esophagitis and Barrett's esophagus and risk factors associated with these diseases.

Material and Methods

Consecutive patients aged 18 years and more and referred for upper endoscopy from primary and secondary settings due to upper gastrointestinal and/or "alarm" symptoms were examined in the Republican Panevėžys Hospital. All the patients were endoscoped with an Olympus Exera videoendoscopy system. Erosive esophagitis was classified according to the Los Angeles classification (9). Targeted biopsies from suspected areas of Barrett's metaplasia were obtained. Barrett's esophagus was diagnosed according to the guidelines of the American College of Gastroenterology (10). Biopsy specimens were taken from each quadrant in each 1-cm segment.

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Barrett's esophagus was defined by the presence of intestinal metaplasia with goblet cells. Barrett's esophagus was classified according to the length of columnar-lined epithelium to short (less than 3 cm above the gastroesophageal junction) and long (at least and more than 3 cm above the gastroesophageal junction) segments. Hiatal hernia size was evaluated on withdrawal of the endoscope and was measured in centimeters.

Of all the endoscoped patients, consecutive patients with erosive esophagitis were included into the separate groups of grade A, B, C, and D esophagitis and Barrett's esophagus. According to our statistical precalculation, inclusion was discontinued when each group contained 40 patients. These selected patients were tested for *H. pylori* using a serological method (HPSC, SureScreen Diagnostics Ltd, United Kingdom), rapid urease test (Pronto Dry, Medical Instruments Corp., Switzerland), and histology (Giemsa staining). *H. pylori* was diagnosed if the results of at least one of the tests were positive. The patients were interviewed.

The study was approved by the Ethics Committee of the Hospital of the Lithuanian University of Health Sciences.

Statistical Analysis. The significance of difference between parametric values was evaluated using the Student *t* test and one-way ANOVA. The significance of difference between 2 nonparametric values was evaluated using the Mann-Whitney *U* and Wilcoxon tests, and comparing more than 2 groups, the Kruskal-Wallis test was employed. Factors associated with the presence of the disease were evaluated by multivariate logistic regression analysis.

Results

Endoscopic Findings. A total of 4032 consecutive patients (mean age, 45.13 [SD, 16.17] years) underwent upper endoscopy: 2431 women (60.4%) and 1596 men (39.6%). Endoscopic examination demonstrated esophageal lesions in 2328 patients (57.7%) (Table 1). Erosive esophagitis was diagnosed in 474 patients (11.75%), with a mean age of 45.6 years (SD, 15.2). Erosive esophagitis was documented significantly more frequently among the male than females patients (n=279, 17.5% vs. n=195, 8.0%; $P<0.001$). Among the patients with erosive esophagitis, grade A erosions were established in 194 (41%), grade B in 167 (35%), grade C in 65 (14%), and grade D in 48 patients (10%). The patients with mild-to-moderate forms of erosive esophagitis (grades A and B) were significantly younger than patients with severe forms of esophagitis (grades C and D) (mean age, 52.67±10.88 years vs. 58.67±11.32 years; $P<0.01$).

Histologically confirmed Barrett's esophagus was diagnosed in 0.82% (n=33) of all endoscoped patients and 6.96% of patients with erosive esophagitis. Among patients with Barrett's esophagus, there were 11 women (33.3%) and 22 men (66.7%), with a mean age of 62.67 (SD, 11.75) years. Men and women with Barrett's esophagus were matched for age (mean age, 62.0 [SD, 13.24] years vs. 63.0 [SD, 11.25] years, $P=0.82$). In 7 patients, Barrett's esophagus was not confirmed histologically. No dysplasia or adenocarcinoma in Barrett's epithelium was found. All the patients with Barrett's esophagus also had erosive esophagitis: grade A, 5 patients (15.2%); grade B, 11 (33.3%); grade C, 10 (30.3%); and grade D, 7 (21.2%).

Short-segment Barrett's esophagus (SSBE) was found in 18 patients (mean age, 59.17±11.82 years; 12 men and 6 women). Long-segment Barrett's esophagus (LSBE) was observed in 15 patients (mean age, 66.87 years, SD, 10.55; 10 men and 5 women). There were no significant differences in the mean age and body mass index (BMI) between the groups, whereas men with LSBE were significantly older than their counterparts with SSBE ($P=0.039$). Hiatal hernia was significantly larger in the patients with LSBE than those with SSBE (3.04±0.66 and 2.37±0.57 cm, respectively; $P=0.011$). *H. pylori* was established in 4 (22.2%) of the 18 patients with LSBE and in 8 (53.3%) of the 15 patients with SSBE ($P>0.05$). The proportions of smokers were similar in both the groups.

Comparison of Patients With Erosive Esophagitis of Different Grades and Barrett's Esophagus. The following analysis was based on selected 193 patients with erosive esophagitis and Barrett's esophagus (mean age, 55.99 years; SD, 12.88). There were 115 men (59.6%) and 78 women (40.4%). The mean age

Table 1. Endoscopic Findings (n=4032)

Endoscopic Finding	No. of Patients	%	Age, Mean (SD), Years
Erosive esophagitis	474	11.75	45.6 (15.2)
Barrett's esophagus	33	0.82	62.7 (11.8)
Erosive gastritis and/or duodenitis	1097	29.1	41.0 (14.7)
Duodenal ulcer	502	12.5	48.7 (14.5)
Gastric ulcer	448	11.1	60.3 (12.0)
Gastric cancer	46	1.1	59.5 (11.9)
Esophageal cancer	12	0.29	67.6 (15.4)
Others (polyps, etc.)	322	7.9	40.6 (12.1)
Normal mucosa or nonspecific signs	1704	42.3	36.3 (15.7)

of male and female patients was 54.8 (SD, 13.17) and 57.44 (SD, 12.43) years, respectively (P=0.13).

Demographic and clinical characteristics, endoscopic findings, and *H. pylori* status of patients with erosive esophagitis of different grades and Barrett's esophagus are presented in Table 2.

The patients with Barrett's esophagus was significantly older than those with grades A, B, and C erosive esophagitis (P<0.05). Patients with mild erosive esophagitis (grades A and B) were significantly younger than those with severe degree (grades C and D) (P<0.05). Men with Barrett's esophagus and grade D erosive esophagitis were significantly older than those with grade B erosive esophagitis (P<0.01).

The mean BMI of patients with GERD was 28.21 kg/m^2 (SD, 3.72). A significant difference in BMI between patients with Barrett's esophagus and those with grade A erosive esophagitis was found (P<0.05).

Of the 193 patients included in the study, 106 (54.9%) were infected with *H. pylori* bacteria. The prevalence of *H. pylori* infection in patients with severe GERD forms (grades C and D erosive esophagitis) and Barrett's esophagus was significantly lower than those having mild GERD forms (grades A and B erosive esophagitis) (P<0.001). Increasing severity of erosive esophagitis and presence of its complication – Barrett's esophagus – were associated with the decreasing prevalence of *H. pylori* (P<0.001) (Table 2).

Hiatal hernia was diagnosed in 175 patients (90.7%). The prevalence of hiatal hernia in the patients with severe erosive esophagitis (grades C and D) and Barrett's esophagus was significantly higher than in the patients with grade A erosive esophagitis (P<0.001) (Table 2). Hiatal hernia was found in all patients (100%) with Barrett's esophagus, in 78 (97.5%) of the 80 patients with severe GERD, and in 64 (80%) of the 80 patients with mild erosive esophagitis (P<0.001). The mean size of hiatal hernia increased with the increasing severity of GERD (erosive esophagitis and Barrett's esophagus) (P<0.05) (Fig.).

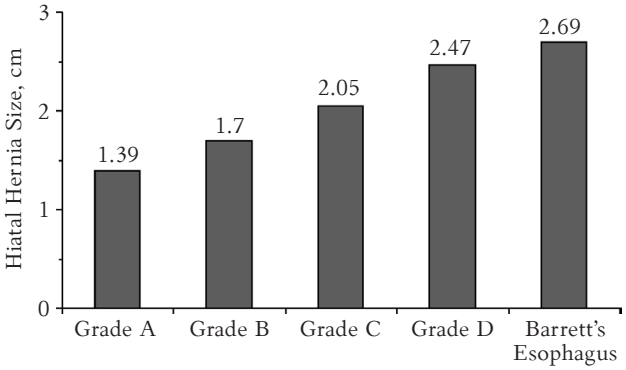

Fig. Hiatal hernia size by different grades of gastroesophageal reflux disease

P<0.05, grade A vs. grade B, C, and D erosive esophagitis and Barrett's esophagus.

Factors Associated With Severe Erosive Esophagitis and Barrett's Esophagus. The factors associated with the development of severe erosive esophagitis (grades C and D) are presented in Table 3. A multivariate logistic regression analysis demonstrated that male gender, absence of *H. pylori*, and hiatal hernia larger than 2 cm in size were independently associated with the development of severe erosive esophagitis. Smoking (>10 cigarettes per day) and age of >60 years were not associated with the development of severe erosive esophagitis.

A multivariate logistic regression analysis revealed that ulcer and/or stricture of esophagus, older age (>60 yrs), smoking (>10 cigarettes per day), hiatal hernia (>2 cm), and absence of *H. pylori* were independently associated with the development of Barrett's esophagus (Table 4).

Table 2. Demographic and Clinical Characteristics of Patients With Different Grades of Erosive Esophagitis and Barrett's Esophagus

Characteristic	Grade A (1)	Grade B (2)	Grade C (3)	Grade D (4)	Barrett's Esophagus (5)	P value
No. of patients	40	40	40	40	33	
Age of men, mean (SD), years	51.23 (14.2)	49.78 (12.9)	53.39 (9.4)	58.48 (13.3)	63.0 (11.25)	$P_{2 \text{ vs. } 4, 5}$<0.01 $P_{5 \text{ vs. } 1, 3}$<0.05
Age of women, mean (SD), years	55.75 (11.5)	61.35 (10.2)	62.09 (12.0)	55.8 (11.62)	62.0 (13.24)	$P_{2 \text{ vs. } 3, 5}$<0.05
Age of all patients, mean (SD), years	54.98 (12.3)	54.7 (13.05)	56.21 (10.9)	57.36 (12.6)	62.67 (11.8)	$P_{5 \text{ vs. } 1, 2, 3}$<0.05
BMI, mean (SD), kg/m^2	27.54 (3.52)	28.67 (3.87)	28.26 (2.67)	28.88 (3.06)	29.33 (3.75)	$P_{1 \text{ vs. } 5}$=0.039
Smokers, n (%)	17 (42.5)	15 (37.5)	18 (52.9)	19 (52.8)	18 (54.5)	>0.05
Hiatal hernia, n (%)	31 (77.5)	33 (82.5)	40 (100)	38 (95)	33 (100)	$P_{1 \text{ vs. } 3, 4, 5}$<0.05
Positive for *H. pylori*, n (%)	31 (77.5)	26 (65)	19 (47.5)	18 (45)	12 (36.7)	$P_{1, 2 \text{ vs. } 3, 4, 5}$<0.01

Table 3. Factors Associated With the Presence of Severe Erosive Esophagitis by Multivariate Regression Analysis

Variable	Odds Ratio	95% Confidence Interval	*P* value
Male gender	3.568	1.199; 10.617	**0.022**
Hiatal hernia >2 cm	3.727	1.601; 8.680	**0.002**
Negative for *H. pylori*	4.236	1.066; 16.837	**0.04**
Smoking >10 cigarettes per day	0.270	0.028; 2.589	0.256
Age >60 years	0.981	0.940; 1.025	0.397
Ulcer and/or stricture of esophagus	7.019	0.624; 48.985	0.115

Table 4. Factors Associated With the Presence of Barrett's Esophagus by Multivariate Regression Analysis

Variable	Odds Ratio	95% Confidence Interval	*P* value
Ulcer and/or stricture of esophagus	11.945	2.507; 41.375	**0.001**
Age >60 years	1.056	1.005; 1.197	**0.031**
Smoking >10 cigarettes per day	4.619	1.013; 12.505	**0.048**
Hiatal hernia >2 cm	5.221	1.861; 14.645	**0.002**
Negative for *H. pylori*	5.602	1.381; 22.720	**0.016**
Body mass index	1.109	0.923; 1.332	0.269
Male gender	1.562	0.258; 1.223	0.146

Discussion

Epidemiologic estimates regarding the prevalence of GERD are mainly based on the assumption that heartburn and/or regurgitation are the indicators of the disease (11–13). A systematic review involved 15 epidemiological studies and found the prevalence of GERD (as defined by at least weekly heartburn and/or acid regurgitation) to be 10% to 20% in the Western world and about 5% in Asia (12). However, patients with objective evidence of GERD (such as esophagitis or Barrett's esophagus) do not always have heartburn (14). Therefore, only endoscopy-based studies can establish the actual prevalence of erosive esophagitis. Assuming that about half of symptomatic GERD patients may have erosions, the prevalence of erosive esophagitis may reach 5% to 10% in the Western world and about 2%–3% in Asia. Very recently, Flameling et al. investigated the patients referred for upper endoscopy to establish the diagnosis. Esophagitis (45%) and hiatal hernia (46%) were the most frequently established diagnoses. Barrett's esophagus was detected in 9.2% of patients (15). In our study, the prevalence of erosive esophagitis in the patients who were referred for upper endoscopy due to complaints or symptoms was 11.75%. It was hardly possible to interview such a large number of patients (n=4032) regarding their GERD symptoms; therefore, the relationship between symptoms and endoscopic findings could not be established. It is noteworthy that our patients were patients recruited from primary and secondary care settings, mainly living in rural areas. The majority of them were referred for upper endoscopy directly by general practitioners. Therefore, the results may be different from those obtained in urban areas or university settings, and the published data usually present the findings of studies carried out at tertiary (university) settings. Our patients may better represent the present situation, as usually more complicated cases are managed at tertiary care level. In Sweden, erosive esophagitis was found in 15.5% of the population that underwent endoscopy (16). In a recently published Chinese study, which enrolled 2580 patients, erosive esophagitis was documented in 4.3% of the patients who underwent endoscopy (17). Therefore, the data suggest that the prevalence of erosive esophagitis in our region is between the prevalences in Northern Europe and Asia.

The prevalence of Barrett's esophagus in the general population varies widely ranging from 0.9% to 4.5% depending in part on the population studied and the definitions used (12, 13). There are scarce data on the prevalence of Barrett's in patients referred for upper endoscopy. It has been reported that the overall prevalence of Barrett's esophagus is only 1.5% in the general population (18) rising to about 2.4% in patients with uninvestigated dyspepsia (19). The data from the United States showed that the prevalence of Barrett's esophagus in patients referred for screening colonoscopy was 6.8% (20). A Swedish study recruited patients from a community sample, and histologically confirmed Barrett's esophagus was found in 1.6% of those who underwent endoscopic screening (21). The prevalence of Barrett's esophagus in our study was quite low (0.82% of routinely endoscoped patients), being much lower as reported in Western countries (18) and comparable with the prevalence reported by a large Chinese study (1.0% of routinely endoscoped patients) (17).

There are numerous studies addressing the risk factors of different forms of GERD. It is well recognized that obesity, smoking, and aging are the risk factors for nonerosive and erosive GERD as

well as Barrett's esophagus (22–26). Hiatal hernia is associated with a high risk of developing esophageal erosions, ulcers, and strictures (27). Avidan et al. stressed the critical role played by hiatal hernia in all grades of erosive esophagitis (28). Our data showed that the presence of hiatal hernia (>2 cm) was strongly associated with severe forms of erosive esophagitis. In a Chinese study, male gender, hiatal hernia, and alcohol consumption were found to be positively associated with erosive esophagitis (17). In the Swedish population, hiatal hernia and obesity remained significant risk factors for nonerosive GERD and erosive esophagitis with or without symptoms (OR up to 14 for erosive esophagitis). Those with active *H. pylori* infection had a higher risk of nonerosive GERD than those without *H. pylori* infection (OR, 1.71; 95% CI, 1.23–2.38) (16). In a German study, the presence of *H. pylori* was associated with a lower risk of erosive reflux disease (6). Although we may find the data showing a negative association of *H. pylori* with the severity of GERD, the role of *H. pylori* negativity remains to be clarified (29). Moreover, the prevalence of *H. pylori* is not frequently investigated in patients with Barrett's esophagus (30, 31). Our study is one of the few studies from Eastern Europe that has compared the prevalence of *H. pylori* among patients with erosive esophagitis and Barrett's esophagus. In our patients, the absence of *H. pylori* was found to be strongly associated with severe forms of erosive esophagitis. Our logistic regression analysis showed that hiatal hernia more than 2 cm in size, the absence of *H. pylori*, the presence of ulcer and/or stricture of the esophagus, age more than 60 years, and heavy smoking (>10 cigarettes per day) were found to be significantly associated with the presence of Barrett's esophagus.

Conclusions

The prevalence of erosive esophagitis was found to be low and the prevalence of Barrett's esophagus was found to be very low among routinely endoscoped patients in primary and secondary (regional) settings in a high *Helicobacter pylori* prevalence rural area. Increasing severity of gastroesophageal reflux disease was associated with the decreasing prevalence of *Helicobacter pylori*. Hiatal hernia greater than 2 cm in size and absence of *Helicobacter pylori* were factors associated with the development of both severe erosive esophagitis and Barrett's esophagus.

Statement of Conflict of Interest

The authors state no conflict of interest.

Erozinio ezofagito ir Bareto stemplės rizikos veiksniai didelio *Helicobacter pylori* infekcijos paplitimo regione

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Raktažodžiai: erozinis ezofagitas, Bareto stemplė, *Helicobacter pylori*, paplitimas.

Santrauka. *Tyrimo tikslas.* Nustatyti erozinio ezofagito ir Bareto stemplės rizikos veiksnius didelio *Helicobacter pylori* (*H. pylori)* infekcijos paplitimo regione.

Tyrimo medžiaga ir metodai. Ištirti 4032 ligoniai, kuriems Respublikinėje Panevėžio ligoninėje buvo atliekama viršutinio virškinamojo trakto endoskopija dėl dispepsijos simptomų. Atskirai analizuoti tyrimo duomenys pacientų, kurių skirtingas erozinio ezofagito laipsnis ir Bareto stemplė (po 40 ligonių kiekvienoje grupėje).

Rezultatai. Erozinis ezofagitas nustatytas 474 (11,75 proc.) ligoniams: A laipsnio – 194 (41 proc.), B laipsnio – 167 (35 proc.), C laipsnio – 65 (14 proc.), D laipsnio – 48 (10 proc.) ligoniams. Infekuotumas *H. pylori* neigiamai koreliavo (p<0.001) su erozinio ezofagito laipsniu ir Bareto stemple. Diafragmos stemplinės angos išvaržos (DSAI) dydis teigiamai koreliavo su sunkesniais erozinio ezofagito laipsniais ir Bareto stemple (p<0,05). Sunkaus ezofagito laipsnio rizikos veiksniai buvo vyriškoji lytis: ŠS – 3,57 (95 proc. PI: 1,12–10,62), DSAI: ŠS – 3,73 (95 proc. PI: 1,60–8,68), *H. pylori* nebuvimas: ŠS – 4,24 (95 proc. PI: 1,07–16,84). Bareto stemplės rizikos veiksniai: stemplės opa ir (ar) striktūra: ŠS – 11,94 (95 proc. PI: 2,51–41,37), amžius >60 metų: ŠS – 1,06 (95 proc. PI: 1,01–1,20), rūkymas (>10 cig/d.): ŠS – 4,62 (95 proc. PI: 1,01–12,5), DSAI (>2 cm): ŠS – 5,22 (95 proc. PI: 1,86–14,64), *H. pylori* nebuvimas: ŠS – 5,60 (95 proc. PI: 1,38–22,72).

Išvados. Ligoniams, kuriems buvo atlikta įprasta viršutinio virškinamojo trakto endoskopija regioninėje ligoninėje didelio *H. pylori* paplitimo regione, nustatėme nedidelį sergamumą eroziniu ezofagitu ir labai mažą sergamumą Bareto stemple. Nustatyta neigiama sąsaja tarp infekuotumo *H. pylori* ir gastroezofaginio refliukso ligos sunkumo.

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