

The Influence of *Helicobacter pylori* Infection on the Prevalence of Endoscopic Erosive Esophagitis

Selahattin Unal, Tarkan Karakan, Ibrahim Dogan, Mehmet Cindoruk and Sukru Dumlu

Department of Gastroenterology, Gazi University, Ankara, Turkey

Keywords

Helicobacter pylori, erosive esophagitis, prevalence, gastroesophageal reflux disease.

Reprint requests to: Tarkan Karakan, MD, Department of Gastroenterology, Gazi University, Bilim Dali 8, Kat Besevler, Ankara, Turkey. E-mail: tkarakan@gmail.com

Abstract

Objectives: This study aimed to determine the frequency of endoscopic esophagitis and *Helicobacter pylori* infection in a large Turkish population over a 6-year period.

Methods: We studied a consecutive series of 14,380 patients who had been newly referred for diagnostic esophagogastroduodenoscopy from 2000 to 2006. The mean age value was 45 ± 10 (18–89) years. All endoscopic findings were retrospectively evaluated. Two antral and two corpus biopsies were taken from patients for rapid urease test. Endoscopic esophagitis was defined as the presence of erosions and/or ulceration. The relationship between erosive esophagitis and various relevant factors was analyzed.

Results: The overall prevalence of endoscopic esophagitis was 7.8% (95% CI, 6.9–8.1). The prevalence of positive rapid urease test was 49% (95% CI, 38–53) in patients with esophagitis and 85% (95% CI, 70–96) in patients without esophagitis ($p < .001$). From 2000 to 2006, the frequency of endoscopic esophagitis and the rate of positive rapid urease test remained unchanged. After adjusting for the effects of mean age, male gender, and percentage of hiatal hernia, there was a 0.785% risk reduction in esophagitis with every 1% increase in the rate of positive rapid urease test result.

Conclusions: The frequency of endoscopic esophagitis is significantly lower in patients with a positive rapid urease test result. This negative correlation with *H. pylori* infection reflects a protective effect of *H. pylori* from endoscopic esophagitis in a Turkish population and deserves further investigation.

Helicobacter pylori infection is recognized to be the most important acquired factor in the etiology of ulcers of the stomach and duodenum. However, the infection does not seem to predispose to gastro-esophageal reflux disease (GERD) and some evidence indicates a possible protective effect. The hypothesis is that the presence of *H. pylori* may protect against the development of GERD by suppressing gastric acidity via the neutralizing effect of bacterial ammonia production and corpus gastritis induced by persistent *H. pylori* infection [1–6]. Moreover, a milder GERD symptom is more frequently observed for patients with particularly virulent species. The epidemiologic association between *H. pylori* and GERD is reported in a meta-analysis of 20 observational studies [7]. A mean prevalence of *H. pylori* of 38.2% was observed in GERD subjects, compared with 49.5% in subjects without GERD. However, most studies are conducted in different countries and the sample size was generally small. A large

cohort of patients is needed to clearly define the association between *H. pylori* and erosive esophagitis.

GERD is common in Western populations. A US population-based study reported that approximately 60% of an age- and gender-stratified sample of 2200 residents of Olmsted County, Minnesota, had intermittently experienced episodes of GERD during the previous 12 months, whereas about 20% had suffered at least weekly episodes [8]. GERD occurs more frequently in Europe and North America than in Asia, but recent studies suggest that the prevalence of GERD in Asia is either increasing or better recognized [9,10].

In contrast, there are conflicting evidences surrounding the *H. pylori* infection with no clinically significant effect on GERD symptoms [11–14]. In some reports, virulent strains did not protect against the development of GERD [15,16]. Moreover, recent prospective studies showed improvement in heartburn or pre-existing reflux esophagitis after *H. pylori* eradication among patients with duodenal

ulcer [17,18]. A potential explanation for the controversial results among studies is that prevalence of *H. pylori* infection and distribution of virulent *H. pylori* isolates differs significantly among various geographic regions [7,19].

Host factors may also influence the interplay between *H. pylori* and GERD. A recent report from Japan indicated that interleukin 1-beta 511-T polymorphism is associated with decreased risk of atrophy and decreased risk of GERD in *H. pylori*-infected subjects [20,21]. Conversely, interleukin 1-beta 511-C polymorphism is associated with increased risk of GERD [21]. These data show that in some genetically predisposed patients, *H. pylori* infection may protect against GERD through induction of gastric atrophy.

In this study, we analyzed the computer-based records of patients that were admitted for upper gastrointestinal endoscopy at Gazi University Gastroenterology Department. We also investigated the rapid urease test results of these patients and its relationship with the endoscopic findings, mainly the erosive esophagitis.

Materials and Methods

Patients

Gazi University, Faculty of Medicine in Ankara is a tertiary center for gastrointestinal diseases and the patient population is in the middle socioeconomic status.

A retrospective review of computerized records was carried out. Computerized records of consecutive patients presenting between January 2000 and April 2006, for upper endoscopy (EGD) were reviewed in a retrospective manner. Computerized database was organized to record patients' demographic features, indications for endoscopy, detailed endoscopy report, endoscopic diagnosis, and results of rapid urease tests. All endoscopy reports are in the electronic format and contain standardized fields such as location, size, number, and other specific descriptions of lesions including a final diagnosis. These fields in the endoscopy report are mandatory, as database system denies recording any endoscopy report with missing data. Among 16,554 endoscopic procedures, 2174 procedures were excluded for reasons of repeated procedure, lack of biopsy for rapid urease test (in case of urgent endoscopies for bleeding, foreign body extraction, invasive procedures, bleeding tendency, etc.). The remaining 14,380 upper gastrointestinal endoscopies were enrolled into the analysis. Endoscopic findings, including Barrett's esophagus, erosive esophagitis, gastric ulcer, duodenal ulcer, and hiatal hernia were noted.

Endoscopy

All upper endoscopies were performed using a GIF100 or GIF130 video endoscope (Olympus, Lake Success, NY,

USA). In our center, endoscopic procedures are performed by trainees under supervision of an experienced supervisor of the endoscopy unit. During EGD, the relationship between the gastroesophageal junction (GEJ) and the squamocolumnar junction (SCJ) was carefully noted. The GEJ was defined as the pinch at the end of the tubular esophagus coinciding with the proximal margin of the gastric folds [22]. Barrett's esophagus was defined as the presence of columnar mucosa in the esophagus with histologic evidence of intestinal metaplasia. The length of Barrett's esophagus was measured as the distance from the incisors to the GEJ minus the distance from the incisors to the most proximal displaced SCJ [23]. The columnar epithelium was carefully inspected for the presence of erosions, nodules, or plaques. The presence of a hiatal hernia was noted, defined in terms of the distance between the GEJ and the diaphragmatic pinch. Erosive esophagitis was defined using the Los Angeles (LA) classification [24]. The stomach and duodenum were carefully inspected for the presence of peptic ulcer disease. Gastric and duodenal ulcers were defined as lesions at least 0.5 cm in diameter, possessing unequivocal depth, and located in any portion of the stomach or duodenal bulb. Two biopsies for *H. pylori* rapid urease test were obtained from the antrum and body in all patients with dyspepsia. Informed consent for endoscopy was obtained from each patient prior to the procedure.

Definitions

Endoscopic esophagitis was defined as mucosal breaks extending proximally from the Z-line [5]. Distal esophageal erythema or hyperemia, congestion, edema, granularity, friability, prominent vascularity, mild irregularity in the squamocolumnar junction, and/or red streaks were not considered to be endoscopic evidence of esophagitis. Similarly, subjects with an isolated salmon-colored mucosal island in their lower esophagus and no squamocolumnar junction involvement were also not considered to have esophagitis. For the purpose of this analysis, esophagitis not associated with other significant upper gastrointestinal lesions, that is, peptic ulcers, gastric and duodenal malignancies, was designated primary esophagitis. Secondary esophagitis was diagnosed when concomitant peptic ulcers or gastric and duodenal malignancies were present. Patients with endoscopic Barrett's esophagus, defined as the presence of columnar epithelium ≥ 3 cm above the gastric folds, were included in the esophagitis group even if esophagitis was not endoscopically present. Short-segment Barrett's esophagus was defined as columnar epithelium not longer than 2 cm. Discrete esophageal ulcer with normal intervening mucosa was coded separately. Hiatal hernia was defined as a

circular extension of gastric mucosa above the diaphragm for > 2 cm. Benign peptic stricture was defined as an esophageal narrowing with smooth tapered appearance. Peptic ulcers were defined as mucosal breaks in the stomach and/or duodenum greater than 0.5 cm in diameter. All upper gastrointestinal cancers were confirmed on histology.

Rapid Urease Test

The biopsy specimens for the rapid urease test were removed from the biopsy forceps with a sterile needle and placed immediately into the rapid urease test (CLOtest™ Delta West Ltd, Perth, Australia) and the results were examined by an experienced observer without knowledge of the clinical details at predetermined intervals over 24 hours. The sensitivity and specificity of rapid urease test (CLOtest™) is 75–98% and 95–100%, respectively [25].

In order to prevent false-negative urease test results, the endoscopic procedure was postponed 4 weeks in patients on regular anti-acid treatment or antibiotics.

Statistical Methods

The prevalence of an endoscopic finding was expressed as the percentage (with 95% CI) of patients with that finding divided by the number of upper gastrointestinal endoscopies performed over that particular period. Between-group differences were assessed using the chi-squared test, Fisher's exact test, independent *t*-test, Kruskal–Wallis test, or Mann–Whitney *U*-test, as appropriate. Multivariable analysis was performed to examine associations within the cohort and to explore the effect of confounding factors on prevalence rates. The rate ratios (RR) and 95% CI for each significant variable were calculated from the coefficients in the logistic regression models. All statistics were analyzed using the Statistical Package for the Social Sciences for Windows (SPSS, Chicago, IL, USA). All tests of statistical significance were two-sided with a *p*-value < .05.

Results

Fourteen thousand three hundred and eighty patients underwent their first upper endoscopy from January 2000 to January 2006. The mean age value was 45 ± 10 (18–89) years. There were 8256 male (57.4%) and 6124 female (42.6%) subjects. The indications for endoscopy included dyspepsia in 8245 patients (57.3%), reflux symptoms and/or pyrosis in 2220 patients (15.4%), anemia and/or positive fecal occult blood test in 1672 patients (11.6%), hematemesis and/or melena in 1422 patients (9.8%), dysphagia, and/or vomiting in 591 patients (4.1%), miscellaneous indications in 230 patients (1.6%).

Table 1 Demographic and clinical characteristics of patients with and without endoscopic esophagitis in 14,380 patients between January 2000–April 2006

	With esophagitis	Without esophagitis	<i>p</i> -value
Number of patients	1122	13258	
Male : Female ratio	748:374 (1.5)	7508:5750	< .001
Age (mean ± SD) (year)	54.0 ± 15.8	50 ± 14.6	< .001
Hiatal hernia	256 (22.8%)	663 (5%)	< .001
Positive rapid urease test	617 (54.9%)	11174 (84.2%)	< .001

Frequency of Endoscopic Findings

The frequency of endoscopic esophagitis was 1122 (7.8%, 95% CI; 6.9–8.1). Of these, 159 patients (14%) had endoscopic esophagitis associated with peptic ulcer or upper gastrointestinal malignancy (secondary esophagitis); the remainder had endoscopic esophagitis with no other significant lesion (primary esophagitis). Demographic and clinical characteristics of patients with and without endoscopic esophagitis are summarized in Table 1. Esophagitis was more frequent in males and older individuals. The prevalence of esophagitis was similar in each year of the study period.

Hiatal hernia was found in 919 patients (81.9% of those with erosive esophagitis) and it was more frequent among patients with esophagitis compared with those without (Table 1). The prevalence of esophagitis was 28.3% (95% CI; 24.6–29.7) in patients with hiatal hernia and 5.3% (95% CI; 3.9–7.1) in those without hiatal hernia (*p* < .001).

In total, there were 2859 subjects (19.8%; 95% CI, 17.5–20.1) who had peptic ulcers (1264 duodenal ulcers, 1393 gastric ulcer, and 202 duodenal plus gastric ulcers). No significant difference in the prevalence of peptic ulcer disease was evident between subjects with and without esophagitis. Gastric malignancy was diagnosed in 244 patients (1.7%, 95% CI; 1.4–1.9) and its prevalence was similar among patients with and without esophagitis.

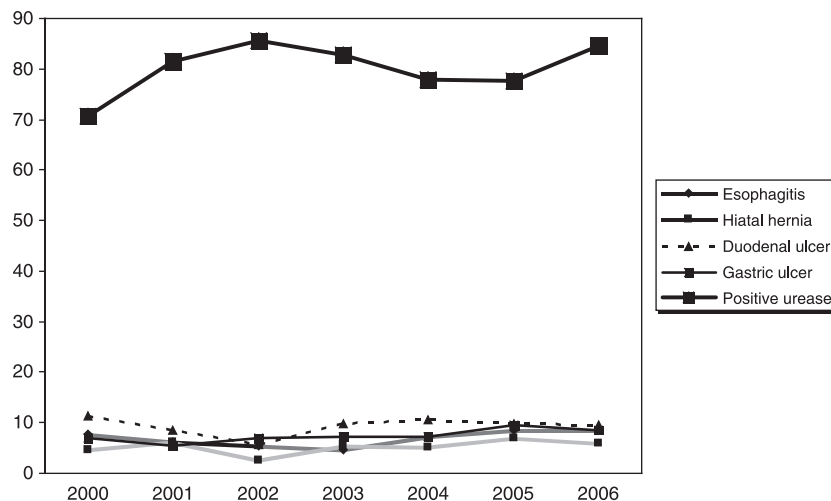
Endoscopic Barrett's esophagus was diagnosed in 223 patients (1.55%; 95% CI, 1.22–1.68). Most of them (186 out of 223, 83.4%) were short-segment Barrett's esophagus. These patients were included in the esophagitis group.

Severe erosive esophagitis (LA classification C and D) rate was 22.5% of those with erosive esophagitis (95% CI, 19.7–24.4).

Prevalence of Positive Rapid Urease Tests

H. pylori infection detected by rapid urease test was positive in 11,791 patients (82%, 95% CI; 77–85). Male subjects (89%, 95% CI; 86.2–90.1) were more likely to have positive

Figure 1 Prevalence rates (x-axis) of endoscopic findings and positive rapid urease test results by year of endoscopy (y-axis) in 14,380 patients between January 2000 and April 2006.



rapid urease test than female subjects (77%, 95% CI: 75.6–80.9; $p < .001$). Positive test results were more likely to be recorded in older subjects (mean age \pm SD: 58.3 \pm 18 year for those with positive results versus 49.5 \pm 11.7 years for those with a negative test result) ($p < .05$).

Patients with endoscopic esophagitis had a lower prevalence of positive rapid urease tests than those without esophagitis (Table 1). The prevalence of esophagitis was 6.4% (95% CI; 5.5–7.3) among patients with positive rapid urease tests compared with 10.1% (95% CI; 9.3–11.2) for those with negative rapid urease tests ($p < .01$). Among patients with hiatal hernia and negative rapid urease tests, the prevalence of endoscopic esophagitis was 30.4% (95% CI; 28.5–32.2), compared with 7.8% (95% CI; 7.1–8.7) in those with positive rapid urease tests but without hiatal hernia ($p < .001$).

The prevalence of positive urease test result in patients with peptic ulcer disease was 92.2% (95% CI; 85.5–99.7). Positive rapid urease test rate was lower in patients with endoscopic Barrett's esophagus (45 of 223, 20%).

Time Trend Changes

The annual prevalence rates among patients undergoing upper endoscopy of esophagitis, hiatal hernia, duodenal ulcer, gastric ulcer, and positive rapid urease tests are illustrated in Fig. 1. Linear regression rates did not reveal any significant trends for increasing rates of esophagitis from 2000 to 2006. The prevalence of positive rapid urease tests also remained unchanged. The prevalence rates of hiatal hernia, duodenal ulcer, gastric ulcer, and age–gender distributions were generally stable over the 6-year period.

Multivariate Analysis

The potential predisposing factors on the frequency of endoscopic esophagitis were evaluated by multivariate

Table 2 Rate ratios (RR) and 95% CI for esophagitis analyzed by logistic regression model in 14,380 patients between January 2000 and April 2006

Variables	RR	95% CI	p-value
Positive rapid urease test	0.79	0.765–0.791	<.01
Male gender	1.45	1.016–1.545	.044
Hiatal hernia rate	1.24	1.212–1.302	<.05
Age	1.03	0.955–1.567	.789

analysis. The prevalence of esophagitis was included as the dependent variable and year of endoscopy as the independent variable. As gender, age, hiatal hernia rate, and positive rapid urease test rate were correlated with esophagitis prevalence in the univariate analysis (Table 1), these predictive variables are sequentially entered into the analysis. The covariates retained significant in the final model were positive rapid urease test, male gender, and hiatal hernia (Table 2). After adjusting for the effects of mean age, male gender, and percentage of hiatal hernia, there was a 0.785% risk reduction in esophagitis with every 1% increase in the rate of positive rapid urease test result.

Discussion

The prevalence of esophagitis in the Eastern part of the world was reported between 6.9 and 14.5% [26,27]. A considerable number of studies have compared the prevalence of *H. pylori* infection in patients with GERD and controls. These studies indicate that prevalence of *H. pylori* infection in patients with GERD is significantly lower than in controls [1,28]. This negative association is less marked in studies performed in the Western world than in the Eastern world [1]. In our study, the prevalence of positive

rapid urease test was lower in patients with endoscopic esophagitis than those without esophagitis (54.9% versus 84.2%). In addition, prevalence of esophagitis was lower in patients with a positive rapid urease test result than patients with a negative rapid urease test result (6.4% versus 10.1%).

There is also some evidence that reflux disease in *H. pylori*-negative patients tends to be more severe than in *H. pylori*-positive patients [28]. In addition, more virulent, cytotoxin-associated gene A (*cagA*)-positive strains of *H. pylori* are associated with less-severe reflux disease [29–31]. All these observations are consistent with *H. pylori* infection providing some protection against the development of reflux disease. However, one weakness in most of the above studies is that they have examined patients who have presented for endoscopy rather than studying a cross-section of the general population.

Ethnic distribution of erosive esophagitis is reported in a study from the Netherlands [32]. A total of 1640 consecutive patients with reflux esophagitis were included. Sixty-one patients were of Turkish descent. Reflux esophagitis occurred significantly more often in ethnically Dutch people (overall 33% versus 9.7%, $p < .001$). *H. pylori* was present in 60.6% of Turkish patients and in 18.5% of Dutch patients. This study shows that certain ethnic groups, irrespective of their geographic localization, are more prone to develop erosive esophagitis and associated *H. pylori* infection is a major contributing factor. The frequency of endoscopic esophagitis in our study (overall prevalence 7.8%) is in accordance with previous reports (6.9–14.5%) [26,27].

The effect of *H. pylori* infection on the occurrence of erosive esophagitis is discussed in a study from Singapore [26]. Similar methodologic approach was used for the evaluation of *H. pylori*-esophagitis association (urease test, retrospective analysis). The rate of endoscopic esophagitis was 7.3% in patients with a positive urease test and 9.0% in those in whom the urease test was negative ($p < .001$). The frequency of endoscopic esophagitis increased, whereas that of positive urease test rate decreased on a yearly basis [26]. This increasing trend in the rate of endoscopic esophagitis was lacking in our study. We did not detect any significant change in the rates of endoscopic esophagitis, duodenal ulcer, gastric ulcer, hiatal hernia, gender distribution, and mean value of age from 2000 to 2006. The steady state of prevalence of esophagitis and *H. pylori* infection may be explained by the increasing rate of clarithromycin resistance [33]. Despite the increased awareness of *H. pylori* infection, eradication rates are still unsatisfactory in the developing world [34]. The *H. pylori* eradication failure may be a significant factor for the steady-state prevalence of esophagitis and *H. pylori* infection in our population.

H. pylori infection rate was lower in our patients with Barrett's esophagus (20%) than patients without esophagitis

(84.2%) ($p < .01$). In a meta-analysis by Gisbert et al. the prevalence of *H. pylori* infection in patients with Barrett's esophagus was lower than the incidence in controls (28% versus 45%. Odds Ratio: 0.6; 95% CI: 0.48–0.76) [35]. However, there are contradictory studies indicating a similar or higher prevalence of *H. pylori* infection in Barrett's esophagus [36,37]. Differences in the rate of *H. pylori* infection in Barrett's esophagus may be related to geographic distribution, ethnic groups, and prevalence of virulent species (*cagA* positive) in different populations [37]. In fact, 72.3% of *H. pylori* isolates from peptic ulcer patients are *cagA* positive in Turkey [38]. The high prevalence of *cagA*-positive species may influence the lower outcome of Barrett's esophagus and erosive esophagitis in our population.

In a prospective multicenter open cohort study of 6215 GERD patients, the independent predictors of erosive GERD as opposed to non-erosive GERD were: male gender, overweight, regular use of alcohol, a history of GERD longer than 1 year, smoking, and a positive *H. pylori* status [39]. In our study, we have investigated erosive GERD patients and in the multivariate analysis, after adjusting for the potential effects of age, male gender, and hiatal hernia, there was a 0.785% risk reduction in esophagitis with every 1% increase in the rate of positive rapid urease test result.

In conclusion, the prevalence of *H. pylori* infection in patients with erosive esophagitis is lower than patients without esophagitis. Lack of *H. pylori* infection is an independent predictor for developing erosive esophagitis and probably for the development of Barrett's esophagus in susceptible patients. However, the exact influence of *H. pylori* on the pathogenesis of GERD is unknown and further studies are needed.

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