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Effect of *Helicobacter pylori* Infection on Duodenitis in Patients with Dyspepsia

Dispepsisi Olan Hastalarda *Helicobacter pylori* Enfeksiyonunun Duodenit Üzerine Etkisi

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ABSTRACT

Objective: *Helicobacter pylori (H. pylori)* infection is one of the principal causes of many gastroduodenal diseases, but its role in duodenitis development is not exactly known. The purpose of this study was to elucidate the role of gastric *H. pylori* infection on clinical, laboratory, and endoscopical features of duodenitis in patients with dyspepsia.

Methods: A total number of 131 patients (77 females and 54 males) were enrolled in the study. The control group was formed from *H. pylori*-negative dyspepsia patients (n=60). Clinical, biochemical, and endoscopical evaluations were performed on all subjects. Biopsies were obtained from the gastric antrum, corpus, and duodenal bulb to detect *H. pylori* and for histopathological assessments.

Results: *H. pylori* infection was positive in 71 patients (54.2%). We detected ulcer-like dyspepsia in 87 patients (66.4%) and dysmotility-like dyspepsia in 44 patients (33.6%). There were no marked differences in biochemical parameters between the groups. On the other hand, there was a marked decrease in ferritin levels in *H. pylori*-positive group (p=0.001). Endoscopical examination showed that the *H. pylori*-positive group had more frequent erosive duodenitis (p=0.039). Villous obliteration and duodenal intraepithelial lymphocytosis as histopathological features were seen more commonly in the *H. pylori*-positive group (p<0.001 for both).

Conclusion: Our data demonsrated that the presence of gastric *H. pylori* infection is one of the components that can influence the endoscopical, histopathological and laboratory features of duodenitis.

Keywords: Duodenitis, *Helicobacter pylori*, dyspepsia, endoscopy, histopathology

ÖZ

Amaç: *Helicobacter pylori* (*H. pylori*) infeksiyonu, birçok gastroduodenal hastalığın başlıca nedenlerinden biridir, fakat duodenit oluşumundaki rolü tam olarak bilinmemektedir. Bu çalışmanın amacı, dispepsili hastalarda duodenitin klinik, laboratuar ve endoskopik özellikleri üzerine gastrik *H. pylori* infeksiyonunun rolünü araştırmaktı.

Yöntemler: Bu çalışmaya toplamda 131 hasta (77 kadın ve 54 erkek) dahil edildi. Kontrol grubu *H. pylori*-negatif dispepsi hastalarından oluşturuldu (n=60). Bütün hastalarda klinik, biyokimyasal ve endoskopik değerlendirmeler yapıldı. H. pylori'yi saptamak ve histopatolojik değerlendirmeler için gastrik antrum, korpus ve duodenal bulbusdan biyopsiler alındı.

Bulgular: *H. pylori* infeksiyonu 71 hastada pozitifti (%5w4,2). Ülser benzeri dispepsiyi 87 hastada (%66,4) ve dismotilite benzeri dispepsiyi 44 hastada tespit ettik (%33,6). Gruplar arasında biyokimyasal parametrelerde anlamlı farklılıklar yoktu. Fakat, *H. pylori*-pozitif grupta ferritin düzeylerinde anlamlı azalma vardı (p=0,001). Endoskopik muayenede *H. pylori*-pozitif grupta daha sık erozif duodenit gözlendi (p=0,039). *H. pylori*-pozitif grupta histopatolojik özellik olarak villus obliterasyonu ve duodenal intraepiteliyal lenfositoz daha çok gözlendi (her iki grup için p<0,001).

Sonuç: Sonuçlarımız gastrik *H. pylori* infeksiyonunun varlığının duodenitin endoskopik, histopatolojik ve laboratuar özelliklerini etkileyebilen unsurlardan biri olduğunu gösterdi.

Anahtar kelimeler: Duodenit, *Helicobacter pylori*, dispepsi, endoskopi, histopatoloji

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INTRODUCTION

Dyspepsia is recurrent and chronic upper abdominal pain or discomfort. It affects up to 40% of the general population and is a significant cause of reduced quality of life among patients (1). Dyspeptic symptoms have been clustered into three categories as follows: ulcer-like dyspepsia in which the predominant symptom is discomfort and pain located in the upper abdomen (most troublesome); dysmotility-like dyspepsia, a bothersome or unpleasant discomfort originating in the upper abdomen associated with upper abdominal fullness, bloating, nausea, or early satiety; and nonspecific/unspecified dyspepsia characterized as the presence of symptoms that do not meet the criteria for dysmotility-like or ulcer-like dyspepsia (2). Recent studies have shown that duodenal mucosal permeability increases in patients with functional dyspepsia (3, 4). Therefore, impaired duodenal mucosal barrier function might contribute to the pathophysiology of dyspepsia.

The presence of *Helicobacter pylori* (*H. pylori*) is one of the leading causes of peptic ulcer, duodenal ulcer, duodenitis, and chronic gastritis. Additionally, *H. pylori* may be associated with various extra-gastrointestinal diseases, such as idiopathic thrombocytopenic purpura, coronary artery disease, unexplained iron deficiency anemia, and ischemic stroke (5). *H. pylori* is a small gram-negative bacillus that inhabits the human stomach and duodenum (6). Its role in producing dyspepsia symptoms is not completely understood. However, duodenitis is often associated with the presence of *H. pylori* (7, 8).

A recent systematic meta-analysis and review has demonstrated that although *H. pylori* prevalence widely varies between regions and countries, more than half the world's population is infected (9). In Turkey, *H. pylori* prevalence has been reported to be very high, estimated as 82.5% in the adult population (10). The goal of this study was to assess the presence of an association between *H. pylori* positivity and endoscopic or histological features of the duodenal mucosa in patients referred for endoscopy to investigate dyspepsia.

METHODS

Study Population

The present study group consisted of 131 adult patients with dyspepsia evaluated at a tertiary medical center. The criteria for inclusion were subjects aged >18 years who underwent endoscopy for dyspepsia. The exclusion criteria were as follows: an evidence of gastroduodenal malignancies, duodenal ulcer, gastric ulcer, or scar on gastroscopy; liver, biliary, or pancreatic diseases on ultrasound examination; the use of corticosteroids, immunosuppressives, proton pump inhibitors, oral anticoagulants, aspirin, antibiotics known to be active against *H. pylori*, or other non-steroidal anti-inflammatory drugs within the preceding 4 weeks; presence of Crohn's disease or Zollinger-Ellison syndrome involving the duodenum; pregnancy; previous upper gastrointestinal surgery; renal or hepatic failure; or other severe concomitant illnesses. Routine clinical and biochemical evaluations were performed on all subjects. Dyspepsia diagnosis was according to the Rome III criteria. The control group included patients with *H. pylori*-negative dyspepsia. The study protocol was reviewed and approved by the local Ethics Committee, and the study was conducted in accordance with the guidelines in the Declaration of Helsinki. Written informed consent was obtained from all patients and volunteers.

Endoscopy and Biopsy Sampling

All patients underwent the routine preparation for endoscopy as follows: fasting for 8 h for liquids and solids. Patients were submitted to 5-10 puffs of 10% lidocaine spray in the oropharynx just before the endoscopy. Endoscopy was performed under intravenous midazolam (0.07-0.1 mg/kg) sedation. A flexible gastroscope (Fujinon EG-250WR5, Saitama, Japan) was used. Sydney classification was employed for endoscopic findings of duodenal morphology, and the severity of endoscopic duodenitis was described as mild, moderate, or severe (11). One gastric antral, one gastric corpus, and four duodenal biopsies were taken from the duodenal bulb during each endoscopic examination. Biopsies were taken through endoscopic biopsy forceps from the mucosa of the duodenal bulb of the patients. Among these biopsies, one antral, one corpus, and one duodenal specimen were used to detect *H. pylori* by the rapid urease test, and the others were used for histological examination.

Histological Analysis

Biopsies were fixed in 10% formalin, embedded in paraffin, and cut in sequential 3-µm sections. For histological examination, sections of the tissue samples were stained with hematoxylin and eosin. Sections were stained with Alcian blue periodic acid-Schiff (AB/PAS) for assessing and identifying the extent of duodenal gastric metaplasia. Sections were also immunostained for CD3 to assess the number of intraepithelial lymphocytes present in each specimen. Histological material was examined by an experienced pathologist who was blinded to clinical and endoscopic tests. Duodenal biopsy specimens were graded according to the updated Sydney System (12). The histological severity of chronic inflammation in mucosa was assessed on a scale of four grades (normal, mild, moderate, and severe) according to the degree of mononuclear cell infiltration. Acute inflammation was characterized as the degree of stromal and epithelial neutrophil infiltration and was also graded as follows: 0, none; 1, mild; 2, moderate; 3, severe.

Data Analysis

Data were presented as percentage or mean±standard deviation. The SPSS (Statistical Package for Sociel Sciences) Version 22.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Unpaired Student's t-test was used for comparisons of the differences between mean values of two groups. The Mann-Whitney U-test was used to detect significant differences between histopathological scores. Chi-squared test was used to analyze frequencies. P-values presented are two-tailed, with a significant level of 0.05.

RESULTS

The age of the patients ranged from 18-85 (mean of 46.0±16.0) years. Among all the patients, 77 (58.8%) were females and 54 (41.2%) were males. The overall *H. pylori* infection prevalence was

54.2% (n=71/131). In total, 87 patients (66.4%) presented with ulcer-like dyspepsia, whereas 44 patients (33.6%) presented with dysmotility-like dyspepsia. In total, 7 (5.3%) patients presented with celiac disease, and 4 (3.1%) presented with duodenal gastric metaplasia.

There were no differences in blood biochemical parameters of the patients with and without *H. pylori* in terms of hemoglobin, hematocrit, mean corpuscular volume, Fe^{2+}, transferrin saturation, total iron binding capacity, vitamin B_{12}, and folic acid levels (Table 1). However, a marked decrease in ferritin levels was noted in the *H. pylori*-positive group (p=0.001).

Based on endoscopic duodenitis classification, there was a high frequency of erosive duodenitis but a low incidence of nodular duodenitis in the *H. pylori*-positive group compared with that in the *H. pylori*-negative group (p=0.039, Figure 1). Based on endoscopic duodenitis classification, there were no significant changes in the distribution of patients with ulcer-like dyspepsia or patients with dysmotility-like dyspepsia (p=0.125, Figure 2). No marked changes were noted in the severity of duodenitis in the *H. pylori*-negative and *H. pylori*-positive groups (p=0.308, Figure 3). Histopathological analysis revealed that there were marked augmentations in both duodenal intraepithelial lymphocytosis and villus obliterations in the *H. pylori*-positive group (p<0.001 for both, Figure 4).

DISCUSSION

In this study, we showed that the frequency of erosive duodenitis was high in *H. pylori*-positive patients. Moreover, augmented duodenal intraepithelial lymphocytosis, villous obliterations, and diminished ferritin levels were detected in *H. pylori*-positive patients. Our results suggest that there is an association between *H. pylori* infection and duodenitis in patients with dyspepsia. The contribution of the presence of *H. pylori* to duodenitis has been previously described in patients with duodenal ulcer (13).

Tablo 1. Characteristics of blood biochemical values of the patients with and without *H. pylori*

Parameters	Patients without *H. pylori* (n=60)	Patients with *H. pylori* (n=71)	p
Hemoglobin (g/dL)	13.3±2.0	13.1±2.1	0.580
Hematocrit (%)	38.9±5.3	38.7±5.5	0.833
MCV (fL)	83.2±8.6	82.2±12.6	0.605
Fe2+ (mg/dL)	57.5±33.1	56.9±35.7	0.921
Total iron binding capacity (mg/dL)	302.3±52.9	304.3±47.8	0.821
Transferrin saturation (%)	18.2±8.9	18.1±10.1	0.953
Ferritin (mg/dL)	84.5±12.3	76.9±13.6	0.001
Vitamin B12 (ng/dL)	305.7±37.6	292.2±41.8	0.056
Folic acid (ng/mL)	9.2±5.3	8.8±6.0	0.689

MCV: mean corpuscular volume

This previous study has indicated that biopsies with regenerative changes demonstrated a significant polymorphonuclear leukocyte infiltration regardless of the duodenal *H. pylori* status. In biopsies with no regenerative changes, *H. pylori* colonization was commonly associated with leukocyte infiltration (13). Other studies have also observed that histological duodenitis is often associated with *H. pylori* (75%-82%) (7, 14). These findings imply that *H. pylori* is another critical factor in the development of lymphocyte and leukocyte infiltration in the duodenal mucosa.

We observed an increased erosive duodenitis in *H. pylori*-positive patients. Few studies have investigated the possible role of and the association between *H. pylori* infection and the appearance of duodenitis. It has been postulated that the presence of endoscopic findings of duodenitis may appear from *H. pylori* infection or from an acid-pepsin attack and is generally associated with histopathologic abnormalities, including gastric metaplasia (15). *H. pylori* increases the production of ammonia in the gastric lumen

Figure 1. Incidences of *H. pylori*-positive and *H. pylori*-negative groups according to endoscopic duodenitis classification *p<0.05

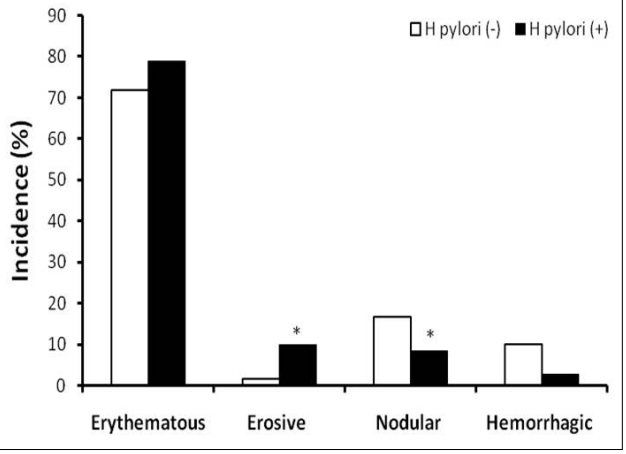
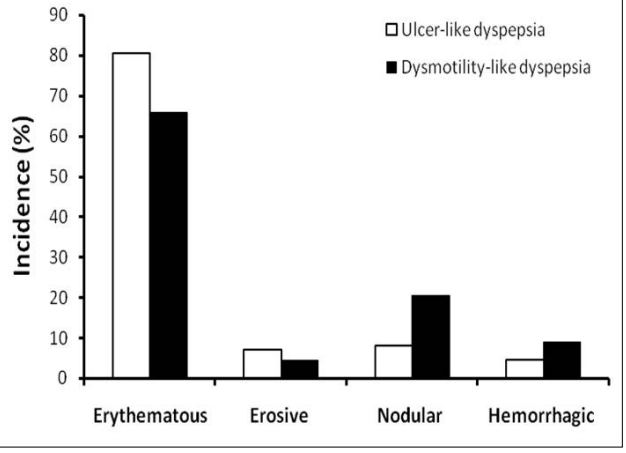


Figure 2. Incidences of patients with ulcer-like dyspepsia or patients with dysmotility-like dyspepsia according to endoscopic duodenitis classification



by its urease activity. Ammonia toxicity may cause cell destruction and the disintegration of cell permeability and active transport (6). Moreover, *H. pylori* produces factors capable of chemoattracting and activating monocytes and neutrophils that induce inflammation (16). The epithelium responds to *H. pylori* infection by mucin depletion, cellular exfoliation, the desquamation of the epithelium, and compensatory regenerative changes (17, 18). *H. pylori* is associated with cytotoxicity on mucosal cells when spread to the duodenal mucosa. *H. pylori*-induced inflammatory injury may stimulate the development of further duodenal gastric metaplasia (13, 17). In contrast, it has been demonstrated that there is an insignificant difference in the severity of endoscopic duodenitis between *H. pylori*-negative and -positive patients (19). Furthermore, effective *H. pylori* eradication has been reported to produce no marked change in endoscopic appearance (19).

Figure 3. Severity of duodenitis in *H. pylori*-positive and *H. pylori*-negative groups

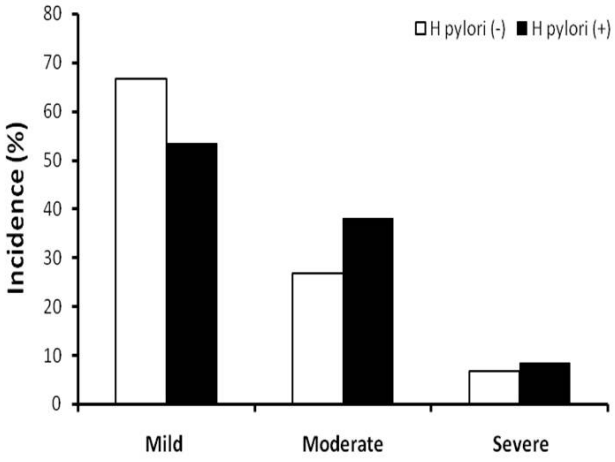
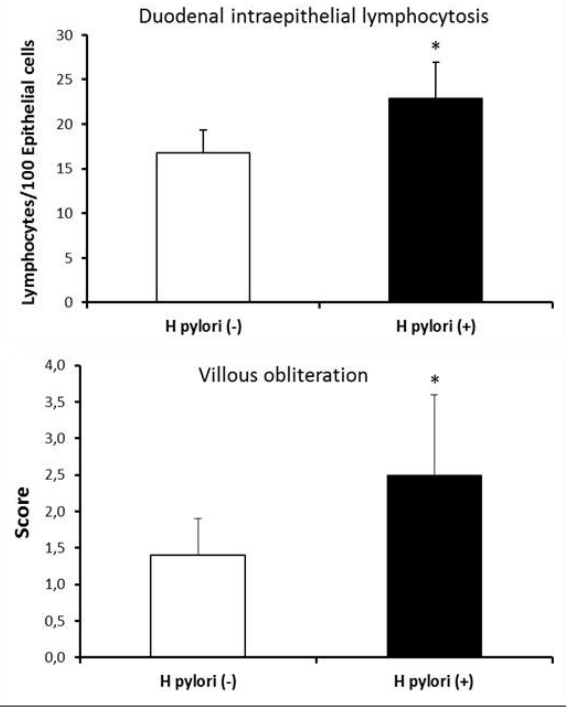


Figure 4. a, b. Duodenal intraepithelial lymphocytosis (a); and villous obliteration (b) in *H. pylori*-positive and *H. pylori*-negative groups *p<0.001 for both



Diffuse nodular duodenitis is a distinctive type of chronic duodenitis. Currently, little is known regarding the mechanism of its pathogenesis. Our data showed that there was a decrease in nodular duodenitis in *H. pylori*-positive patients. Reasons underlying this reduction are not known. Li et al. (20) have shown that neither the acid suppression treatment nor *H. pylori* eradication can significantly change the appearance of endoscopic nodular duodenitis. Therefore, the presence of *H. pylori* infection may not be associated with nodular duodenitis.

In the present study, there were increases in villus obliterations in the *H. pylori*-positive group. These data support the previous observations that reduction in villus size, increased cellular infiltrate, and mucosal architecture abnormalities are noted in biopsies from visually inflamed areas of nonspecific duodenitis (21, 22). Collectively, these findings may suggest that impaired duodenal mucosal barrier function can contribute to the pathophysiology of duodenitis and dyspepsia.

We observed that *H. pylori* infection is accompanied with diminished serum ferritin levels. Although there is significant heterogeneity among the studies, a recent meta-analysis has demonstrated that serum ferritin levels increased as a consequence of *H. pylori* eradication treatment (23).

CONCLUSION

The findings of this study provided updated information and indicated that the presence of gastric *H. pylori* infection is one of the components that can contribute to the endoscopic, histopathological, and laboratory features of duodenitis. Therefore, the determination of the degree of morphological changes associated with *H. pylori* infection in dyspepsia is valuable in the treatment and follow-up of patients. Further investigations of effects of *H. pylori* infection on duodenitis in large prospective studies would be helpful in understanding the pathogenesis of duodenitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kocaeli University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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