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ORIGINAL ARTICLE

Helicobacter pylori colonization density may have an important role in the development of celiac disease

Helicobacter pylori kolonizasyon yoğunluğu çölyak hastalığının gelişmesinde önemli rol oynayabilir

Mevlüt KIYAK, Tolga DÜZENLİ

Department of Gastroenterology, Health Science University, Prof. Dr. Ilhan Varank Training and Research Hospital, Istanbul, Turkey

Background and Aims: The aim of this study was to investigate the relationship between celiac disease and *Helicobacter pylori* infection and to compare the severity of celiac disease and *Helicobacter pylori* infection in adults according to the modified Marsh score. **Materials and Methods:** This study included 148 patients with celiac disease and 240 control patients without celiac disease who underwent endoscopy for various reasons in a tertiary hospital. Age, gender, endoscopy indications, descriptive characteristics, complaints, serological, endoscopic and histopathological findings of the patients were recorded and analyzed. **Results:** *Helicobacter pylori* colonization in the celiac disease patients was 43.9% and in control group was 57.5% (p = 0.009). *Helicobacter pylori* positivity rate was significantly lower in Marsh 2, 3A, 3B, 3C groups (p = 0.04). Pearson correlation analysis revealed a significant but weak negative relationship between the severity of *Helicobacter pylori* and celiac disease (r = -.109, p = 0.031). When Marsh score was increasing, *Helicobacter pylori* grade decreased. **Conclusion:** The current study indicated that the incidence of *Helicobacter pylori* infection was lower in adults with celiac disease compared to control patients, and *Helicobacter pylori* colonization density was associated with milder duodenal lesions in celiac patients. *Helicobacter pylori* colonization may have a protective role in the development of celiac disease.

Key words: Celiac disease, endoscopic findings, *Helicobacter pylori*, Marsh score

Giriş ve Amaç: Bu çalışmanın amacı çölyak hastalığı ile *Helicobacter pylori* enfeksiyonu arasındaki ilişkiyi araştırmak ve modifiye Marsh skoruna göre erişkinlerde çölyak hastalığı ile *Helicobacter pylori* enfeksiyonunun şiddetini karşılaştırmaktır. **Gereç ve Yöntem:** Bu çalışmaya 3. basamak bir hastanede tanı alan 148 çölyak hastası ve çeşitli nedenlerle endoskopi yapılan 240 kontrol hastası dahil edildi. Hastaların yaş, cinsiyet, endoskopi endikasyonları, tanımlayıcı özellikleri, şikayetleri, serolojik, endoskopik ve histopatolojik bulguları kaydedildi ve analiz edildi. **Bulgular:** Çölyak hastalarında *Helicobacter pylori* kolonizasyonu %43.9, kontrol grubunda %57.5 idi (p = 0.009). *Helicobacter pylori* pozitiflik oranı Marsh 2, 3A, 3B, 3C gruplarında anlamlı olarak daha düşüktü (p = 0.04). Pearson korelasyon analizi, *Helicobacter pylori*'nin şiddeti ile çölyak hastalığı arasında zayıf ancak anlamlı negatif bir ilişki ortaya koydu (r = -.109, p = 0.031). Marsh skoru arttıkça *Helicobacter pylori* derecesi düştü. **Sonuç:** Mevcut çalışma, çölyak hastalığı olan erişkinlerde kontrol hastalarına göre *Helicobacter pylori* enfeksiyonu insidansının daha düşük olduğunu ve *Helicobacter pylori* kolonizasyon yoğunluğunun çölyak hastalarında daha hafif duodenal lezyonlarla ilişkili olduğunu göstermiştir. *Helicobacter pylori* kolonizasyonu, çölyak hastalığının gelişiminde koruyucu bir role sahip olabilir.

Anahtar kelimeler: Çölyak hastalığı, endoskopik bulgular, *Helicobacter pylori*, Marsh skoru

INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disease that involves the proximal small intestine, triggered by exposure to gluten in genetically predisposed individuals, accompanied by autoimmune reactions mediated by T cells (1). The prevalence of CD has been reported to be approximately 1% in the USA and European countries, and it has been stated that there has been an increase in the risk of CD in the last 50 years (2,3).

While some of the environmental factors are blamed as risk factors for the development of CD; a number of environmental factors have been asso-

Correspondence: Mevlüt KIYAK • Department of Gastroenterology, Prof. Dr. Ilhan Varank Training and Research Hospital, Namık Kemal Cd. No:7, 34785, Istanbul, Turkey • Phone: +90 216 606 33 00 • Fax: +90 216 606 3395 • Email: drmkiyak@gmail.com • *Kıyak M, Düzenli T. • Helicobacter pylori colonization density may have an important role in the development of celiac disease • The Turkish Journal of Academic Gastroenterology 2023;22:06-12.* ***Doi: 10.17941/agd.1271863***

ciated with a reduced incidence of CD in a limited number of studies. One of these environmental factors was *Helicobacter pylori (H. pylori)* infection (4). However, conflicting results have been reported in the literature regarding *H. pylori* for the risk of CD (5-7). On the other hand, several recent studies reported that *H. pylori* infection is not only associated with pathologies of gastroduodenal discomfort; but also plays an important role in some non-gastric diseases (8,9).

The aim of this study was to investigate the relationship between CD and *H. pylori* infection and to compare the severity of CD and *H. pylori* infection in adults according to the modified Marsh score.

MATERIALS and METHODS

Study Population and Design

This study included 148 patients over the age of 18 who underwent endoscopy with a preliminary diagnosis of CD and 240 control patients without CD who underwent endoscopy for various reasons between 1th February 2018 and 1th Fabruary 2022 in a tertiary hospital. The local ethics committee approved the study (the protocol number that was attributed by the ethics committee Prof. Dr. Ilhan Varank Sancaktepe Hospital, Health Science University of was: 00163385893/50, and the date of approval by the ethics committee was 12 April 2022), which was carried out following the Declaration of Helsinki, 1964, and later revisions.

Celiac antibody [tissue transglutaminase immunoglobulin A (Ig A) antibody] positivity was confirmed in all patients. At the diagnosis, Ig A deficiency was ruled out. Age, gender, endoscopy indications and descriptive characteristics of the patients were recorded. Clinical complaints, serological findings, endoscopic findings and pathology reports of the cases were reviewed retrospectively. Patients known to have received eradication therapy for *H. pylori* and patients with insufficient biopsy sampling were excluded from the study. In the study, antrum and corpus biopsy preparations of the patients were stained with hematoxylin eosin and modified Giemsa dyes and examined under light microscopy. Preparations were evaluated for *H. pylori* as none (-), low (+), moderate (++), and high (+++) according to bacterial density by Sydney classification.

Modified Marsh classification (Marsh-Oberhuber) was used for the diagnosis of celiac disease. The patients were classified as Marsh 1, Marsh 2, Marsh 3A, Marsh 3B, Marsh 3C. All cases were evaluated and reported by two experienced pathologists.

Statistical Analysis

Statistical analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc., Chicago, USA). Continuous data were defined as mean ± standard deviation, while categorical data were defined as percentages. The median value was used for the variables that did not show normal distribution. Fisher's exact test for categorical variables and Student's t test for numerical variables were used to evaluate statistical differences between patients in the celiac patient and control groups. In statistical analysis, correlations were evaluated with Pearson's correlation coefficient. $P < 0.05$ was considered statistically significant.

RESULTS

There were 148 patients in the celiac group and 240 patients in the control group. 72.3% (n = 107) of the patients were women in the celiac group; and 64.2% (n = 154) control group. Mean age of celiac group was 33 ± 9.5 years and control group was 34 ± 8.1 years (Table 1). In the CD group, the youngest patient was 18 years old and the oldest patient was 62 years old. There was no statistically significant difference between the two groups in terms of mean age ($p = 0.251$). Chronic diarrhea (43.9%) in the CD

group and dyspeptic complaints (61.3%) in the control group were the most common indications for endoscopy. Antral gastritis, pangastritis, peptic ulcer and mass was found to be significantly lower in the celiac group than in the control group in terms of endoscopic findings (p = 0.014) (Table 2).

H. pylori colonization in the celiac group was 43.9% and 57.5% in the control group (p = 0.009) (Table 3). When Marsh 2, 3A, 3B, 3C groups were evaluated in celiac patients, the *H. pylori* positivity rate was significantly lower in each group than the control patients (p = 0.04) (Table 4). Pearson correlation analysis revealed a significant but weak negative relationship between the severity of *H. pylori* and CD (r = -.109, p = 0.031). In celiac patients, when celiac Marsh score was increasing, *H. pylori* grade was decreased.

Table 1 Comparison of demographic data, admission complaints and laboratory results between groups.

		Celiac Disease			Control Group			
		N	%	Mean	N	%	Mean	p
Sex	Male	41	27.7%		86	35.8%		0.098
	Female	107	72.3%		154	64.2%		
Age		148		33 (±9)	240		34 (±8)	0.251
Symptoms	Diarrhea	65	43.9%		14	5.8%		**< 0.001**
	Weight loss or inability to gain	4	2.7%		17	7.1%		
	Dyspepsia or GERD	46	31.1%		147	61.3%		
	Stomach ache	2	1.4%		18	7.5%		
	Abdominal distention, indigestion	5	3.4%		23	9.6%		
	Anemia, low ferritin or vitamin deficiency	19	12.8%		21	8.8%		
	Antibody positivity	7	4.7%		0	0.0%		
Hemoglobin (gr/dL)				11.1 (± 2)			13 (± 2)	**< 0.001**
Ferritin (ng/mL)				13 (7*)			41 (26*)	**< 0.001**

* Median was used instead of standard deviation for independent data showing nonparametric distribution. Pearson chi-square test was used to compare categorical variables, and independent Student's T test was used to compare parametric variables. P < 0.05 was considered statistically significant.
GERD: Gastroesophageal reflux disease.

Table 2 Comparison of endoscopic diagnoses between groups.

	Celiac Disease		Control Group		
	N	%	N	%	p
Normal	30	20.3%	1	0.4%	**0.014***
Antral gastritis	35	23.6%	66	27.5%	
Pangastritis	39	26.4%	86	35.8%	
Bulbus ulcer	11	7.4%	27	11.3%	
Gastric ulcer	0	0.0%	2	0.8%	
Hiatal hernia, LES failure	16	10.8%	29	12.1%	
Esophagitis	17	11.5%	25	10.4%	
Mass lesion	0	0.0%	4	1.7%	

*p <0.05 was considered statistically significant. LES: Lower esophageal sphincter.

Table 3 Presence and degree of *H. pylori* between groups.

		Celiac Disease		Control Group		
		N	%	N	%	p
H. pylori presence	*H. pylori* (-)	83	56.1%	102	42.5%	**0.009***
	H. pylori (+)	65	43.9%	138	57.5%	
H. pylori grade	*H. pylori* (-)	83	56.1%	102	42.5%	**0.017***
	H. pylori (+)	36	24.3%	61	25.4%	
	H. pylori (++)	17	11.5%	55	22.9%	
	H. pylori (+++)	12	8.1%	22	9.2%	

*p <0.05 was considered statistically significant.

Table 4 The relationship between CD Modified Marsh score and *H. pylori*.

Celiac Score (Modified Marsh Score)	Presence of *H. pylori*				
	H. pylori (+)		*H. pylori* (-)		
	N	%	N	%	p
Normal duodenal biopsy	128	63.1%	96	51.9%	**0.04***
Intraepithelial lymphocyte (> 40/100 enterocytes)	11	5.4%	5	2.7%	
Crypt hyperplasia (Marsh 2)	15	7.4%	20	10.8%	
Mild villus atrophy (Marsh 3A)	38	18.7%	45	24.3%	
Middle villus atrophy (Marsh 3B)	8	3.9%	15	8.1%	
Total villus atrophy (Marsh 3C)	3	1.5%	4	2.2%	

*p <0.05 was considered statistically significant

DISCUSSION

This study revealed a negative significant relationship between CD and *H. pylori* infection. In addition, duodenal damage was less common in celiac patients in the presence of *H. pylori* infection. When the *H. pylori* density increased, duodenal damage (according to the modified Marsh classification) had decreased. This inverse relationship between CD and *H. pylori* supported the idea that *H. pylori* infection may have a protective effect in terms of CD (4).

There are prevalence studies in the literature in which the diagnoses of *H. pylori* infection were made serologically (6,10,11). In the studies of Crabtree et al. in the adult CD group and Luzza et al. in the pediatric CD group, the prevalence of *H. pylori* was not different from the control group (10,11). Konturek et al. reported an increased *H. pylori* seroprevalence among patients with the diagnosis of CD, suggesting a potential possible relationship between *H. pylori* virulence and CD (6). In addition, Jozefczuk et al. reported that the incidence of *H. pylori* in the pediatric patient group diagnosed by urea breath test was similar to the control group (12). The fact that histopathology was not used in the diagnosis of *H. pylori* in these studies can be considered a handicap, because the gold standard for the diagnosis of *H. pylori* is histopathological evaluation (13). Later on, studies on histopathological diagnosis increased in the literature. Rostami-Nejad et al. compared dyspep-

tic and celiac patients in two similar studies conducted consecutively (14,15). In their first study in 2009, they included serology and histology and in the second study in 2011, they conducted the study based on histology. In both studies, the prevalence of *H. pylori* was not statistically different between the two groups.

On the other hand, there are studies suggesting that *H. pylori* infection may be protective against celiac disease. Ciacci et al. evaluated the prevalence of *H. pylori* in the adult CD group and found the incidence of *H. pylori* to be significantly lower in the CD group (5). Lebwohl et al. reported the incidence of *H. pylori* in the CD group significantly lower for all age groups (4). They also evaluated the effect of *H. pylori* infection on duodenal damage in the same study. The prevalence of *H. pylori* was 4.2% in the Marsh 3A group, and 4.5% in the Marsh 3B/3C group (4). In Villanacci et al's study of 80 *H. pylori* -infected celiac patients, milder duodenal damage was observed (16). In another study with adult patients, the percentages of *H. pylori* in Marsh grade 1/2 and grade 3 lesions were 50% and 33%, respectively. This finding supported that the rate of *H. pylori* infection was higher in lower grade CD patients (17). This result brought up the possibility that the presence of *H. pylori* infection may alleviate the duodenal damage in the CD group. However, that was not confirmed by the multicenter study of Bayrak et al. They found *H. pylori* infection to be significantly lower in CD patients, yet the presence of *H. pylori* was not associated with duodenal damage (18). A meta-analysis consisted of 25 studies (12 with adult patients, 13 with pediatric patients) suggested that *H. pylori* infection might be a protective factor in celiac disease, since the prevalence of *H. pylori* infection was found to be lower in celiac patients than in the control group (19).

Studies investigating the relationship between *H. pylori* and dudeonal damage have been based on the Marsh classification. Comparisons were made by recategorizing the Marsh classification. In studies comparing the Marsh 1/2 and Marsh 3 groups, statistically insignificant differences were found between the two groups (7,16,18,20). There are also studies in which Marsh 3 is categorized within itself. Although there was a difference between the two groups comparing Marsh 3A/B and C, this difference was still not statistically significant (18,21-23). Yue et al. reported in their meta-analysis that the presence of *H. pylori* infection did not affect the celiac classification in these studies (19). In the current study, the prevalence of *H. pylori* infection was lower in the celiac disese group, and in this respect, it was compatible with Yue et al's meta-analysis (19). However, the most important difference of our study was that *H. pylori* infection affected the modified Marsh classification in CD patients. In our study, we performed separate analyzes for Marsh 2, 3A, 3B and 3C without categorizing and combining the Marsh classification, and evaluated the *H. pylori* rates. Correlation analysis had been used to reveal the possible relationship between the presence of infection and the degree of duodonal damage in the CD group. According to the modified Marsh score, we found a lower *H. pylori* positivity rate in 2, 3A, 3B and 3C. In the subsequent correlation analysis, there was a significant weak-negative relationship between *H. pylori* density and CD severity. In other words, we noticed that duodenal damage (according to the modified Marsh score) had decreased as the *H. pylori* density increased in CD patients. As Amlashi et al. mentioned in their meta-analysis, which is consistent with our study, this negative relationship may mean a protective role of *H. pylori* in celiac patients (24).

There are some opinions on this subject in the literature. It has been reported that chronic *H. pylori* infection may alter the T-cell response and this may result in a decrease in the incidence of CD.

This condition was stated by Lebwohl et al. as the 'hygiene hypothesis' (4). On the other hand, *H. pylori* -induced regulatory T cells in the gastric mucosa can affect the cellular response to gluten in the intestinal wall, and that *H. pylori* can modulate and reduce gastroduodenal permeability (25). In addition, Caminero et al. proposed that *H. pylori* could alter the immunogenicity of ingested gluten through modification of gastric pH or cross-talk between them (26). Although all these claims are unclear for now; it makes sense that the incidence of CD would be lower in patients with *H. pylori* infection, and duodenal damage may be less common in patients infected with *H. pylori*.

One of the limitations of our study was that socioeconomic factors such as ethnicity, household size, low family income, and inadequate living conditions were not taken into account in our study. Despite our limitations, one of the strengths of our study was that the relationship between duodenal damage and the presence of *H. pylori* was evaluated by correlation analysis. In addition, the diagnosis of *H. pylori* infection was made histologically, and patients who had taken antibiotics in the last 1 month before the procedure were excluded from the study. Another strength of our study was the use of clinical, serological, endoscopic and histopathological parameters in the diagnosis of CD.

In conclusion the current study indicated that the incidence of *H. pylori* infection was lower in adults with CD compared to control patients, and *H. pylori* colonization was associated with milder duodenal lesions in CD patients. This may suggest that *H. pylori* colonization has a protective role in the development of CD. However, since some conditions such as the socioeconomic status of the patients were not evaluated in the study, the interpretation of the results should be done carefully. Systematic, large-scale, cohort studies are required to clarify the causal relationship between *H. pylori* infection and celiac disease.

Ethics: *This study was approved by Prof. Dr.Ilhan Varank Sancaktepe Hospital, Health Science University, Ethics Committee on April 12, 2022, with the number 00163385893/50.*

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