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Original Article NEPHROLOGY

Is duodenal biopsy appropriate in areas endemic for *Helicobacter pylori*?

Abdurrahman Sahin,[1] Gulcin Cihangiroglu,[2] Yilmaz Bilgic,[1] Turan Calhan[3], Mustafa Cengiz[4]

[1]Department of Gastroenterology, Elazig Training and Research Hospital, Elazig, Turkey

[2]Department of Pathology, Elazig Training and Research Hospital, Elazig, Turkey

[3]Department of Gastroenterology, Private Turkey Hospital, Istanbul, Turkey

[4]Department of Gastroenterology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

ABSTRACT

OBJECTIVE: The primary reason for obtaining duodenal biopsy sample is to diagnose celiac disease. *Helicobacter pylori* (*H. pylori*) and drug injury are common causes of duodenitis. The aim of this retrospective study was to explore effects of *H. pylori* and drugs on duodenal mucosa.

METHODS: Duodenal biopsy samples of patients who underwent upper gastrointestinal endoscopy (UGIE) between February 2014 and December 2014 were retrospectively examined. Clinical symptoms, referral indications, endoscopic findings, *H. pylori* status, and drug history were recorded. Duodenal biopsy findings were compared based on presence of *H. pylori* and drug history.

RESULTS: Of 2389 patients who underwent UGIE, 206 had duodenal biopsy. Eight patients (3.9%) were diagnosed with celiac disease. After excluding cases with celiac disease, 76 patients of remaining 198 patients (36.9%) had duodenal histopathological abnormality. *H. pylori* was found in 95 (47.9%) patients. Drug usage was less common (42%). Of patients who had histopathological duodenitis, 59% were *H. pylori*-infected. Rate of duodenitis was higher in *H. pylori* (+) group than in *H. pylori* (-) group (45% vs 27.1%; odds ratio, 2.4; 95% confidence interval, 1.3–4.4; p=0.005). There was no difference between groups regarding drug use in terms of histopathological duodenitis.

CONCLUSION: *H. pylori* is the major contributor to duodenitis in high prevalence regions. Serological testing may be more appropriate before performing duodenal biopsy in patients with suspected celiac disease.

Keywords: Acetylsalicylic acid; celiac disease; duodenitis; Helicobacter pylori; nonsteroidal anti-inflammatory drugs.

Upper gastrointestinal endoscopy (UGIE) is a common procedure to investigate dyspepsia, dysphagia, and other upper gastrointestinal (GI) symptoms [1]. Inspection of duodenum is one of the basic components of routine upper GI endoscopic examination. Duodenal endoscopic findings give important clues for a wide range of disorders affecting upper GI tract.

Duodenal biopsy sample is commonly obtained to investigate iron deficiency anemia, malabsorption, neoplasia, and infectious enteritis. However, various other disorders, such as infectious disease, inflam-

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Correspondence: Dr. Abdurrahman SAHIN. Elazig Egitim ve Arastirma Hastanesi, Gastroenteroloji Klinigi, Elazig, Turkey.
Tel: +90 424 - 212 27 17 e-mail: arahmansmd@yahoo.com

Table 1. Grading criteria of duodenal biopsies according to definitions of Serra et al. [5]

Definition	Criteria
Number and site of biopsy specimens	
Villous height and architecture	Normal, broad, or blunted
Ratio normal villous to crypt (V:C)	Range from 3:1 to 5:1
Surface enterocytes	Normal, flattened, or damaged
Brush borders	Preserved or lost
Presence of crypt hyperplasia	Present/Absent
Intraepithelial lymphocyte count	Range from 1:5 to 5:5
(per 100 epithelial cells)	Normal (1:5) / Increased (range from 2:5 to 5:5)
Gastric metaplasia in chronic duodenitis	Present/Absent
Presence of microorganisms	*Giardia, Cryptosporidium, Microsporidia, Isospora belli, Cyclospora, Mycobacterium avium-intracellulare, Cytomegalovirus, Cryptococcus neoformans*
Neoplasia	Presence of benign or malignant tumor (adenoma or carcinoma, carcinoid, lymphoma)

matory disorder, toxic or physical reactions, may cause duodenal mucosal injury and result in appearance of duodenitis on endoscopic examination [2].

Determination of the cause of duodenitis is important, but histopathological findings do not always correlate with endoscopic findings. It is thought that *Helicobacter pylori* (*H. pylori*) and injury due to use of pharmaceutical drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA) and other antiplatelet drugs, are common cause of duodenitis [3, 4].

The aim of this retrospective study was to evaluate duodenal biopsy samples taken from patients who underwent endoscopic examination. Correlation of histopathological findings with *H. pylori* and drug toxicity was also assessed.

MATERIALS AND METHODS

Patient data

This retrospective study was carried out using data of consecutive patients who underwent endoscopic examination for several indications, including dyspepsia, anemia, chronic diarrhea, epigastric pain, and reflux symptoms, in the gastroenterology department of Elazig Training and Research Hospital (Turkey). Endoscopy records from February 2014 through December 2014 were examined for patients who had duodenal biopsy performed. Endoscopic duodenitis was detected according to presence of erythema, edema, or erosion. Endoscopic findings compatible with celiac disease, such as nodularity, mosaic pattern, and scalloping, were also recorded as endoscopic duodenitis. Demographic and medical data of patients were obtained from hospital databases. Drug prescription data for evaluation of patients in terms of drug usage, especially NSAIDs, ASA, or other antiplatelet drugs, were also obtained from hospital records. In patients who were diagnosed as celiac disease, serological markers, including IgA and IgG antibodies against tissue transglutaminase (tTG), endomysial antibodies (EMA), and gliadin antibodies (AGA), were also recorded. Patients who had inadequate demographic or clinical data or inadequate drug history were excluded.

Histopathological assessment

Duodenal biopsy samples were assessed by one expert pathologist (GC) who was blinded to endoscopic findings. Histopathological findings were evaluated according to definition and classification of duodenal biopsy findings by Serra et al. to ensure objective criteria (Table 1) [5]. Diagnosis of *H. pylori* infection was based on results of rapid urease

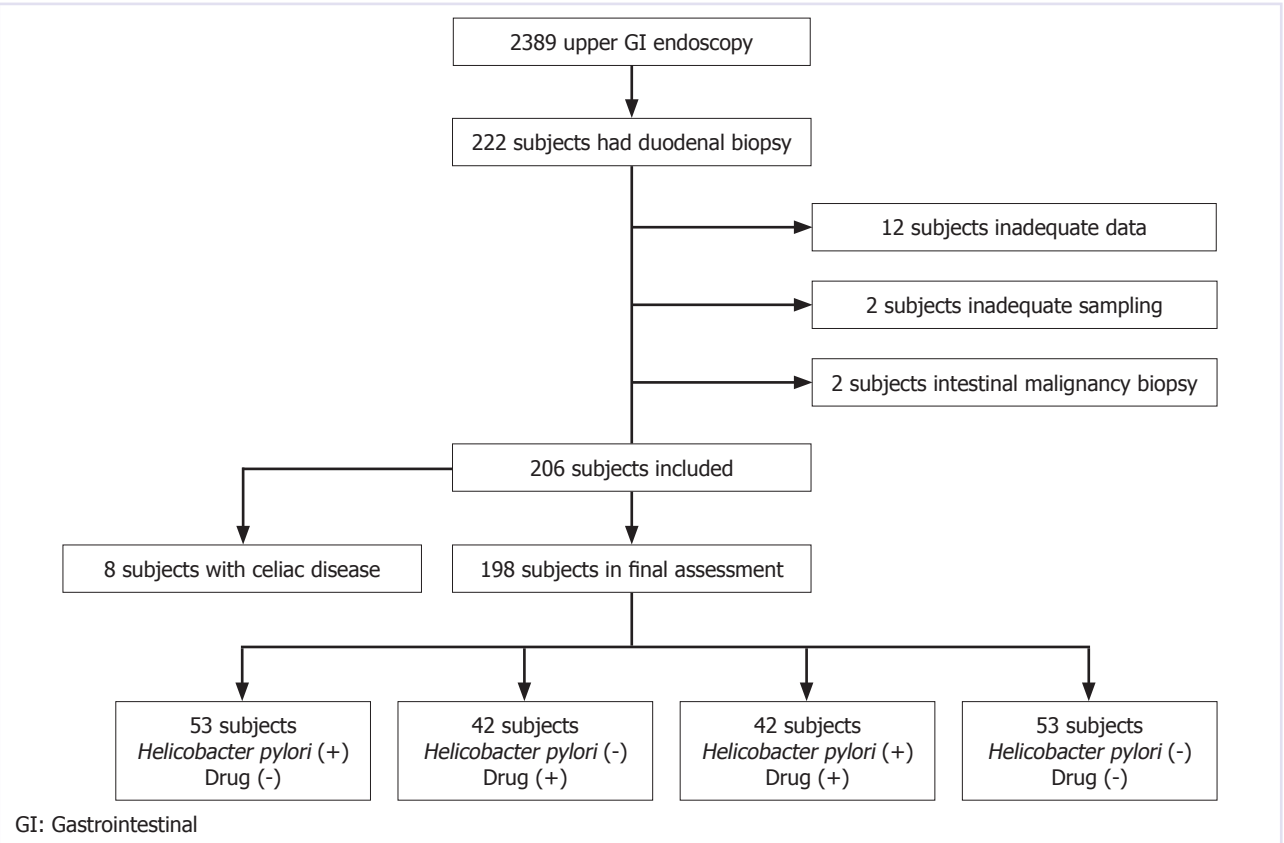

FIGURE 1. Participation flowchart. Patients in final assessment were adjusted according to presence of *Helicobacter pylori* and drug usage.

test or positive identification of the bacteria either on routine stains (Wright-Giemsa stain) or immunostain of gastric biopsies. Histological changes in patients diagnosed with celiac disease were classified according to Marsh classification [6]. Patients who had inadequate duodenal sampling were excluded. Patients diagnosed as malignancy with histopathological assessment of duodenal biopsy samples were also excluded.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA) software. Quantitative data were expressed as mean±SD, while nominal data were expressed as number (percent). Chi-square test and simple odds ratio (OR) (95% confidence interval [CI]) were performed. P value <0.05 was considered significant.

RESULTS

Total of 2389 upper GI endoscopy reports were screened. Among those, 222 patients (9.3%) had duodenal biopsy sampling performed. Clinical data of 12 patients were inadequate and those patients were excluded. Two patients were excluded because samples were either inadequately oriented or were distorted during processing. Two cases were diagnosed as intestinal malignancy (1 carcinoid tumor, 1 ampullary carcinoma). In all, 206 duodenal biopsy samples were accepted for final analysis (Figure 1).

Duodenitis was found in 170 patients (82.5%) as endoscopic finding. Duodenal biopsy sample was taken from remaining 36 patients (17.5%) to investigate anemia (iron deficiency and/or vitamin B12 deficiency) in 26 (12.6%) and/or chronic diarrhea in 11 (5.3%), and intestinal lymphangiectasia in 8 patients. Demographic and clinical features, referral

Table 2. Demographic characteristics, UGIE indications and endoscopic findings of the study population

	Total (n=206)	
	n	%
Age, years (mean±SD)	44.7±17.5	
Gender, female	126	61.2
Helicobacter pylori presence	100	48.5
Drugs‡	88	42.7
Referral indication		
Epigastric pain	90	43.7
Dyspepsia	29	14.1
Regurgitation	10	4.9
Nausea/vomiting	7	3.4
Weight loss	6	2.9
Dysphagia	6	2.9
Chronic diarrhea	11	5.3
Abdominal pain	9	4.4
Anemia	26	12.6
Gastrointestinal bleeding	8	3.9
Endoscopic findings		
LES relaxation	82	39.8
Hiatal hernia	16	7.8
Erythematous antral gastritis	24	11.7
Erythematous pangastritis	131	63.6
Erosive gastritis	40	19.4
Gastric ulcer	4	1.9
Duodenal ulcer	4	1.9

LES: Lower esophageal sphincter; UGIE: Upper gastrointestinal endoscopy. ‡Use of nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, other antiplatelet drugs.

Table 3. Histopathological findings of study population

	Total (n=206)	
	n	%
Pathological abnormality	76	36.9
Villous height and architecture		
Normal	187	90.8
Broad	11	5.3
Blunted	8	3.9
Villous to crypt ratio (V:C)		
3:1	4	1.9
4:1	37	18.0
5:1	163	79.1
Surface enterocytes		
Normal	186	90.3
Flattened	9	4.4
Damaged	11	5.3
Presence of crypt hyperplasia	54	26.2
Intraepithelial lymphocyte increase	68	33.0
Gastric metaplasia in chronic duodenitis	18	8.7
Presence of microorganisms	0	0

indications, and endoscopic findings are presented in Table 2. Pathological abnormalities were seen in 76 patients (36.9%). Most common pathological abnormality was increase in intraepithelial lymphocyte (IEL) count, detected in 33% (n=68) of patients. Second most frequent pathological finding was crypt hyperplasia, established in 54 cases (26.2%). No microorganism was detected in study population. Histopathological assessment of duodenal biopsies is provided in Table 3.

Eight patients (3.9%) were diagnosed as celiac disease according to endoscopic, serological, and histopathological findings (Table 4). Six of them (75%) were female. Mean age was 38.25±16.6 years. Referral indications were epigastric pain in 3 cases, dyspepsia in 1, diarrhea in 2, diarrhea with abdominal pain in 1, and anemia with vitamin B12 deficiency in 1 patient. *H. pylori* was present in 5 patients (67.5%). Duodenitis was prominent finding of endoscopic examination in all patients with celiac disease. Histopathological findings were consistent with Marsh III classification in 6 patients (75%). Duodenal biopsies of 2 patients (25%) were classified as Marsh II.

After exclusion of cases with celiac disease, 198 patients were assessed for influence of *H. pylori* presence or drug use on development of duodenitis. Table 5 is a summary of histopathological findings with respect to *H. pylori* and drug usage. Unique difference was presence of pathological abnormality between groups (p=0.04). There was no difference between groups in subclassification of pathological abnormality (all p>0.05). In subgroup analysis, pathological abnormality was more common among patients who

Table 4. Demographic, clinical, and serological data, UGIE indications of patients with celiac disease, and histopathological findings according to Marsh classification

	Age	Sex	Symptoms	Endoscopic findings	*H. pylori* status	Drug history	Serological positivity marker	Duodenal pathological findings
1	37	M	Abdominal pain, diarrhea	Hiatal hernia, antral gastritis, duodenitis	+	+	AGA IgA, tTG IgA	Marsh IIIA
2	33	F	Anemia	Duodenitis	+	–	tTG IgA	Marsh IIIC
3	24	F	Diarrhea	Pangastritis, duodenitis	–	–	EMA IgA	Marsh II
4	66	F	Diarrhea	Pangastritis, duodenitis	+	+	EMA IgA	Marsh II
5	24	F	Epigastric pain	Antral gastritis, duodenitis	+	–	AGA IgA, tTG IgA	Marsh IIIA
6	24	M	Epigastric pain, regurgitation	Pangastritis, duodenitis	–	+	EMA IgA, tTG IgA	Marsh IIIB
7	61	F	Epigastric pain	Esophagitis, Gastric ulcer, duodenitis	+	+	EMA IgA, tTG IgA	Marsh IIIB
8	37	F	Dyspepsia	LES relaxation, duodenitis	–	–	EMA IgG, tTG IgA	Marsh IIIC

AGA: Anti-gliadin antibody; EMA: Endomysial antibody; F: Female; LES: Lower esophageal sphincter; M: Male; tTG: Tissue transglutaminase antibody; UGIE: Upper gastrointestinal endoscopy.

Table 5. Duodenal histopathological findings regarding *Helicobacter pylori* infection and drug usage

	H. pylori (+) drug (-) (n=53)		*H. pylori* (-) drug (+) (n=42)		*H. pylori* (+) drug (+) (n=42)		*H. pylori* (-) Ddug (-) (n=61)		p
	n	%	n	%	n	%	n	%	
Pathological abnormality	26	49.1	13	30.1	14	33.3	15	24.6	**0.04**
Villous height and architecture									0.85
Normal	48	90.6	40	95.2	40	95.2	58	95.1	
Broad	4	7.5	2	4.8	2	4.8	2	3.3	
Blunted	1	1.9	0	0	0	0	1	1.6	
Villous to crypt ratio (V:C)									0.55
3:1	1	1.9	1	2.4	0	0	1	1.6	
4:1	12	22.6	4	9.5	9	21.4	8	13.1	
5:1	40	75.5	37	88.1	33	78.6	52	58.2	
Surface enterocytes									0.18
Normal	46	86.8	40	95.2	40	95.2	58	95.1	
Flattened	4	7.5	2	4.8	2	4.8	0	0	
Damaged	3	5.7	0	0	0	0	3	4.9	
Presence of crypt hyperplasia	18	34.0	11	26.2	10	23.8	12	19.7	0.37
Intraepithelial lymphocyte increase	23	43.4	13	30.9	11	26.2	14	22.9	0.11
Gastric metaplasia in chronic duodenitis	5	9.4	2	4.7	6	14.2	4	6.4	0.41

Table 6. Duodenal histopathological findings with respect to the presence of *Helicobacter pylori* after excluding patients with celiac disease

	H. pylori (+) (n=95)		*H. pylori* (-) (n=103)		Odds ratio (95% CI)	p
	n	%	n	%		
Pathological abnormality	40	45	28	27.1	**2.4 (1.3–4.4)**	**0.005**
Villous height and architecture						0.61
Normal	88	92.6	98	95.1		
Broad	6	6.3	4	3.9		
Blunted	1	1.0	1	1.0		
Villous to crypt ratio (V:C)						0.13
3:1	1	1.0	2	1.9		
4:1	21	22.1	12	11.6		
5:1	73	76.8	89	86.4		
Presence of crypt hyperplasia	28	29.5	23	22.3	1.5 (0.8–2.8)	0.25
Surface enterocytes						0.27
Normal	86	90.5	98	95.1		
Flattened	6	6.3	2	1.9		
Damaged	3	3.2	3	2.9		
Intraepithelial lymphocyte count					1.6 (0.9–2.9)	0.14
Normal	61	64.2	76	73.8		
Increased	34	35.8	27	26.2		
Gastric metaplasia in chronic duodenitis	11	10	6	5.8	2.1 (0.8–5.9)	0.15
Presence of microorganisms	0	0	0	0		

CI: Confidence interval.

were infected with *H. pylori* and without drug use than in patients without *H. pylori* infection and with drug usage (49.1% vs 24.6%; OR, 2.9; 95% CI, 1.3–6.5; p=0.007). In the same manner, rate of IEL increase was higher in patients who were only infected with *H. pylori* and without drug use than patients without *H. pylori* infection and drug usage (43.4% vs 22.9%; OR, 2.5; 95% CI, 1.1–5.7; p=0.02).

In total, *H. pylori* was found in 95 (47.9%) cases. Histopathological duodenitis was more common among patients infected with *H. pylori* compared to *H. pylori* negative group (45% vs 27.1%; OR, 2.4; 95% CI, 1.3-4.4; p=0.005). Of those with histopathological duodenitis, 59% were *H. pylori* positive (Table 6). No difference was seen between groups according to IEL count, presence of crypt hyperplasia, villus atrophy, or gastric metaplasia (all p>0.05).

Total of 84 patients (42%) were taking NSAID or ASA. Among those patients, 61 (73%) were using proton pump inhibitor at time of UGIE and 42 (50%) showed *H. pylori* positivity. When cases were evaluated according to drug usage, mean age of patients taking NSAID or ASA was higher than mean age of non-users (51.5±16.5 years vs 40.6±16.6 years; p=<0.001). There was no difference between those taking NSAID or ASA and nonusers according to presence of duodenitis, IEL count, presence of crypt hyperplasia, villus atrophy, or gastric metaplasia (all p>0.05).

DISCUSSION

Histological findings of the small intestine are well defined. Investigations of abnormalities in histo-

logical findings have focused on celiac disease, in particular. Histopathological appearance of many diseases affecting duodenum is similar, so details in these findings are often not useful tools for diagnosis and management of diseases affecting the duodenal mucosa.

In this study, we investigated duodenal biopsy findings. However, we found that only 9.3% of patients who underwent endoscopic examination had duodenal biopsy sampling. Reason for sampling in most cases was endoscopic appearance of duodenal mucosa compatible with duodenitis. Other reasons were investigation of anemia, diarrhea, weight loss in setting of normal-appearing mucosa, and presence of intestinal lymphangectasia. Ratio of duodenal biopsy sampling has been reported in the literature to be between 10% and 12% among adult cases undergoing UGIE [7]. Our findings were consistent with these results.

Studies evaluating duodenal histopathological assessment generally focus on presence of celiac disease, and so most were conducted with patients who had normal-appearing mucosa. In a large series, it was found that duodenal biopsies were taken from normal-looking mucosa in 43% of patients who underwent UGIE due to anemia, diarrhea, or weight loss [8]. In nationwide study from the USA that was carried out on 103385 patients for 12-month period, duodenal biopsy sampling rate was 27.2% [9]. An interesting result of that study was that endoscopic appearance of duodenitis, scalloping or erosion/ulcer, were detected in only 5.6% of whole patient population and in 8.5% of patients who had duodenal biopsy. Moreover, 79.5% of duodenal biopsies in study were evaluated as normal histopathological findings. In our study, duodenal biopsies were performed mostly due to endoscopic findings of duodenitis, and only 12.5% of patients who had duodenal biopsy had normal-appearing duodenal mucosa. Endoscopic/histopathological consistency was seen in 36.9% of patients who had duodenal biopsy.

Taking biopsy from patients who had endoscopic appearance of duodenitis is seen as more reliable compared with patients who had normal duodenal endoscopic findings. Diagnostic yield from biopsy sample obtained from normal-appearing mucosa is lower than result of current study. It should also be kept in mind that, although endoscopic/histopathological concordance is well established in esophageal and gastric lesions, agreement between duodenal endoscopic findings and histopathological findings is poor.

In clinical practice, main purpose of duodenal biopsy sampling is frequently to catch or to exclude silent or overt celiac disease. It is still diagnostic gold standard for celiac disease [10]. Eight patients (3.9%) were diagnosed with celiac disease in current study. All of these patients had endoscopic appearance compatible with celiac disease. Our result is consistent with a long-period study from Canada [11]. In that study, celiac disease prevalence was 2.4% among 9665 patients for over 30-year period. In another large-scale study conducted by Carmack and collagenous et al., celiac disease was detected in 1.2% of duodenal biopsy samples. Of patients who had clinical and endoscopic suspicion of celiac disease, 12% were diagnosed with the disease in histopathological assessment, and 64% of these patients had normal histopathological findings.[9]. In this study, celiac disease was diagnosed in 3.0% of those with diarrhea, weight loss, or anemia, and in 1.5% of patients with dyspepsia or gastroesophageal reflux disease. An interesting finding of our study was that referral indications for UGIE were gastrointestinal symptoms, such as epigastric pain and dyspepsia, in half of the patients diagnosed with celiac disease.

Based on results of the above studies and our findings, patients with anemia, weight loss, or diarrhea would all have low probability of having celiac disease at initial clinical assessment. Moreover, endoscopic appearance of duodenitis is not sufficient to make decision on celiac disease. Given limitations of biopsy, including interindividual variability in interpretation and challenges of appropriate sample handling, preferred approach should be to evaluate serological markers prior to endoscopic examination for GI symptoms or other malabsorption-related symptoms (diarrhea, weight loss, anemia). Thus, unnecessary biopsy can be avoided.

Current study demonstrated *H. pylori* positivity of 48% in study population, most of whom were

diagnosed endoscopically as duodenitis. *H. pylori* prevalence has been reported to range from 71.3% to 82.5% in studies from Turkey [12, 13]. Lower prevalence of *H. pylori* in current study population may have been due to high rate of drug usage and affect on gastric and duodenal mucosa.

It is well known that NSAIDs and ASA are important causes of gastroduodenal lesions, especially in *H. pylori* (-) patients [14, 15]. Aside from NSAID-induced gastric mucosal damage, harmful effects of NSAIDs and ASA on intestinal mucosa are well established with widespread use of intestinal examination [16, 17]. A study evaluating patients with obscure GI bleeding showed that ulcerative lesions were due to chronic NSAID use, and mostly located in the ileum. ASA and other antiplatelet drugs cause erosions in all parts of small intestine (jejunum and ileum) [18]. Data about effect of NSAIDs on duodenal mucosa are conflicting. In 1 study, NSAIDs were found to be responsible for only 13% of *H. pylori* (-) duodenal ulcers [15]. Lewis et al. demonstrated that although NSAID drug use was associated with endoscopic appearance of duodenitis, impact of NSAIDs on histological inflammation was minimal [2]. Alternatively, histological changes were prominent in *H. pylori*-infected patients who had normal endoscopic appearance. This explains why histological findings did not differ between groups taking NSAID/ASA and nonusers in current study.

Mirbagheri et al. demonstrated that *H. pylori* infection had close association with histological duodenitis [3]. *H. pylori* presence was 67.3% in their study, and duodenitis was detected in 82.2% of patients infected with *H. pylori*. In an earlier study, histological duodenitis was found to be integral part of *H. pylori* gastritis [19]. Although we found lower presence of *H. pylori* (47.9%) when compared with mentioned studies, it is demonstrated in current study that *H. pylori* presence was major contributor to histopathological duodenitis, as 59% of those with histopathological duodenitis were infected with *H. pylori*.

Gastric metaplasia develops in response to increased duodenal acid load, and has been found with high frequency in *H. pylori*-infected patients, at prevalence of 55% in duodenal ulcer patients and about 25% in those with distal gastric ulcer [1, 20]. High acid load is key event causing development of gastric metaplasia. Gastric metaplasia is considered adaptive event in response to high acid exposure [19]. Genta et al. demonstrated that *H. pylori* gastritis was lower in patients with gastric metaplasia without inflammation (6.3%) than in patients with normal duodenal histology (9.8%) [21]. They concluded that high rate of *H. pylori* negativity among patients with gastric metaplasia without inflammation would open role of *H. pylori* in development of gastric metaplasia to discussion. Contrary to that study, we found that although it did not reach statistical significance, gastric metaplasia was more prevalent among patients who had positive test for *H. pylori*.

Most common pathogenic microorganism detected in duodenal biopsy is Giardia lamblia. In a study, Giardia lamblia was detected in 0.45% of 2000 patients undergoing UGIE [22]. Another study from Turkey reported that 2% of patients with iron deficiency anemia had Giardia lamblia detected in duodenal biopsies [23]. We found no microorganisms in duodenal biopsies of our unselected population. This might be due to small size of our study population.

Major limitation of this study is its retrospective nature. Although duodenal biopsies were revaluated, presence of *H. pylori* was determined according to the pathology reports and endoscopy reports. To standardize pathological assessment, samples were evaluated according to single standard system by one expert pathologist. Clinical and demographic data, including drug usage, were obtained from hospital records and public health insurance system records. Non-prescription drug usage, especially non-prescription NSAIDs, could not be determined due to retrospective nature of this study and use might be underestimated. In this study, although pathological abnormality was more common in *H. pylori*-infected patients, effect of *H. pylori* on abnormality subgroups did not reach statistical significance in our population. However, further studies are needed to evaluate effects of *H. pylori* on duodenal mucosa in terms of histopathological abnormality

subgroups. This study was a single center study conducted in eastern Turkey. Thus, our results cannot be accepted as having universal validity for Turkish population.

In conclusion, duodenal biopsy endoscopic/histopathological concordance is lower than of esophageal and gastric cases. Although most common purpose of duodenal biopsy is diagnosis of celiac disease, histopathological findings rarely direct specific diagnosis. Biopsy of duodenum has low diagnostic yield. *H. pylori* is main cause of duodenitis in regions where it is prevalent. Routine duodenal biopsy for endoscopic appearance of duodenitis in areas endemic for *H. pylori* is not most reasonable approach. Checking serological markers before UGIE is more accurate method to manage appearance of endoscopic duodenitis.

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