

Common Findings in Endoscopic Gastric Biopsies in Southeastern Anatolia: Effects of Eating Habits and *Helicobacter Pylori* Infection

Güneydoğu Anadolu'da Mide Endoskopik Biyopsilerinde Sık Rastlanan Bulgular: Beslenme Alışkanlıklarının ve *Helicobacter Pylori* Enfeksiyonunun Etkisi

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ABSTRACT

Introduction: Roasted and spicy food (mainly hot pepper) consumption is very common in Southeastern Anatolia. Smoked and spicy diets and *Helicobacter pylori* (*H. pylori*) infection are known risk factors for gastric cancer. The aim of this study was to investigate the effects of eating habits on the gastric mucosa, to investigate the rate of *H. pylori* positivity, and to examine the association of these factors with histopathological features in this region.

Methods: Histopathological findings in endoscopic biopsies of 943 consecutive patients were retrospectively evaluated.

Results: More than half of the patients were female (54%; n=505), and the median age was 47±17.27 (range: 18-96). The most common non-gastritis histopathologic diagnosis was gastric carcinoma (2.5%; n=24), followed by polypoid lesions (1.6%; n=16). The vast majority of patients (92%) had chronic gastritis, and neutrophilic activity was present in 61% (n=537). The frequencies of atrophy, intestinal metaplasia, and regenerative mucosal changes were significantly correlated with the severity of neutrophilic activity (p<0.05). Patients with atrophy and intestinal metaplasia were significantly older than those without atrophy and intestinal metaplasia (p<0.001; mean age: 47 and 46 vs 56 and 55, respectively). More than 50% were infected with *H. pylori* (57%; n=542), and *H. pylori* positivity was associated with the presence of chronic and chronic active gastritis, as well as lymphoid hyperplasia (p<0.001). In contrast, erosion, atrophy, and neuroendocrine cell hyperplasia were less common in patients with *H. pylori* gastritis (p<0.05).

Conclusion: *H. pylori* infection and spicy food consumption are key risk factors for gastritis in Southeastern Anatolia. Prospective epidemiological studies are needed to better demonstrate the causal interaction between dietary factors and gastritis.

Keywords: Eating habits, endoscopic biopsy, gastritis, *Helicobacter pylori*, histopathology

ÖZ

Amaç: Közlenmiş ve baharatlı yemekler Güneydoğu Anadolu Bölgesi'nde sık tüketilmektedir. Tütsülenmiş ve baharatlı besinler ile *Helicobacter pylori* (*H. pylori*) enfeksiyonunun mide kanseri için risk faktörü olduğu bilinmektedir. Bu çalışmanın amacı; Güneydoğu Anadolu'da beslenme alışkanlıklarının mide mukozasına etkisini, *H. pylori* pozitifliğini araştırmak ve bu faktörlerin histopatolojik özelliklerle ilişkisini değerlendirmektir.

Yöntemler: Ardışık 943 hastada mide endoskopik biyopsilerindeki histopatolojik özellikler retrospektif olarak değerlendirildi.

Bulgular: Olguların çoğu kadındı (%54; n=505) ve ortalama yaş: 47±17,27 ydi (yaş aralığı: 18-96). Gastrit dışı en sık tanı gastrik karsinom (%2,5; n=24) ve gastrik polipti (%1,6; n=16). Olguların büyük kısmında (%92) kronik gastrit ve bunların %61'inde (n=537) nötrofilik aktivite mevcuttu. Atrofi, intestinal metaplazi ve rejeneratif mukozal değişiklikler nötrofilik aktivitenin derecesi ile anlamlı düzeyde ilişkiliydi (p<0,05). Atrofi ve intestinal metaplazisi olan olgular, olmayanlara göre, anlamlı düzeyde daha yaşlıydı (p<0,001; ortalama yaş sırasıyla; 47 ve 46'ya karşı ve 56 ve 55). Olguların %57'si (n=542) *H. pylori* pozitif ve *H. pylori* varlığı kronik ve kronik aktif gastrit ve lenfoid hiperplazi varlığı ile anlamlı düzeyde ilişkiliydi (p<0,001). Öte yandan; erozyon, atrofi ve nöroendokrin hücre hiperplazisi *H. pylori* gastriti olan bireylerde daha az orandaydı (p<0,05).

Sonuç: *H. pylori* enfeksiyonu ve baharatlı (acı) yiyeceklerin sürekli tüketilmesi Güneydoğu Anadolu'da yaşayan bireylerde gastrit oluşumu için anahtar faktörlerdir. Beslenme alışkanlıkları ile gastrit arasındaki nedensellik ilişkisinin tam olarak gösterilebilmesi için prospektif epidemiyolojik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Beslenme alışkanlığı, endoskopik biyopsi, gastrit, *Helicobacter pylori*, histopatoloji



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Introduction

In Southeastern Turkey, people often consume roasted and spicy food such as roasted hot peppers and red meat directly exposed to heat and flames. While polycyclic hydrocarbons in overcooked meat is considered carcinogenic, there is no consensus on the possible carcinogenic and anticarcinogenic effects of capsaicin, the active ingredient in hot peppers (1-4). Smoked, spicy, and salty diets are widely known to be risk factors for gastric cancer. It has even been suggested that eating habits may affect the course of *Helicobacter pylori* (*H. pylori*) infection, which is another important risk factor for gastric cancer; however, this association remains to be fully elucidated (5).

The aim of this study was to investigate the effects of eating habits on the gastric mucosa, display the histopathologic features, determine the *H. pylori* positivity rate, and investigate the association between these parameters in a population in southeastern Turkey.

Methods

The study protocol was approved by the Adiyaman University Faculty of Medicine Institutional Ethics Committee (approval no: 2017/9-8, date: 19.12.2017). Informed consent was not sought due to the retrospective nature of the study. The endoscopic biopsies of 943 consecutive patients (adults) who were diagnosed in our center between January 01, 2015 and December 31, 2016 were reviewed for the presence/absence of the following findings: acute and/or chronic inflammation, atrophy, metaplasia, erosion, ulceration, dysplasia, regenerative changes, neuroendocrine cell hyperplasia, *H. pylori*, lymphoid hyperplasia (LH), and malignancy. LH was defined as reactive lymphoid follicles forming germinal centers in the lamina propria. Gastritis, atrophy, metaplasia, and *H. pylori* density were scored using the Sydney system (6,7). For better demonstration of intestinal metaplasia and *H. pylori* infection, periodic acid Schiff-Alcian blue (Dako, California, USA) and Warthin Starry (Dako, California, USA) stained slides were reviewed. Clinical data were obtained from patient files.

Statistical Analysis

Statistical analysis was performed using the software SPSS Statistics, Version 24.0 (Armonk, NY: IBM Corp). Non-parametric tests (χ^2 to compare frequencies; Kruskal-Wallis test to compare independent

variables between two groups) and descriptive analyses were used. Results were considered significant at $p < 0.05$.

Results

More than half of the patients were female (54%; $n=505$), and the median age was 47 ± 17.27 (range: 18-96). The most common clinical diagnosis (75%; $n=706$) was gastritis, and the gastric antrum (83%; $n=783$) was the most common biopsy location (Table 1).

The vast majority of patients (92%) had chronic gastritis, and neutrophilic activity was present in 61% ($n=537$) (Figure 1A, B). The severity of chronic inflammation decreased significantly with age, and gastric ulcer was more common in older patients ($p < 0.001$). The frequencies of atrophy, intestinal metaplasia, and regenerative mucosal changes were significantly correlated with the severity of neutrophilic activity, and foveolar hyperplasia was also more common in patients with

Table 1. Clinical characteristics of the study group

Median age	47±17.27 (range: 18-96)
Gender	
Female	54% (n=505)
Male	46% (n=438)
Clinical (endoscopic) diagnosis	
Gastritis	75% (n=706)
Ulcer	3.5% (n=33)
Erosion	5% (n=49)
Suspicion of malignancy and/or dysplasia	7% (n=68)
Atrophy	1% (n=9)
Intestinal metaplasia	1% (n=9)
Polyp/polypoid lesion	2.8% (n=26)
Biopsy location*	
Antrum	83% (n=783)
Corpus	12% (n=116)
Fundus	1.2% (n=11)
Cardia	0.7% (n=7)
Pylorus	0.7% (n=7)
Other/unknown	3% (n=26)
*Some patients had multiple biopsies from different locations	

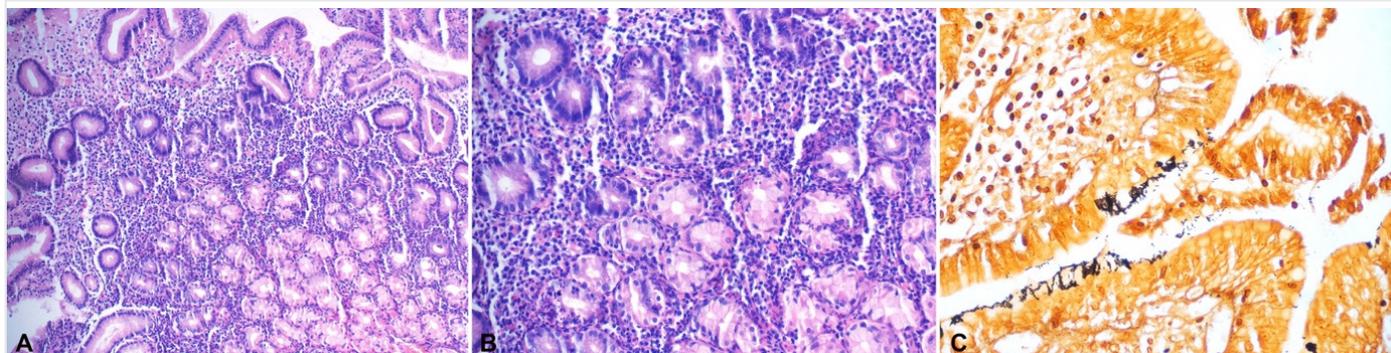


Figure 1. Chronic gastritis was the most common finding, with neutrophilic activity present in more than half of the patients. A-B) Mixed inflammatory cells within the lamina propria, also infiltrating occasional glands. Hematoxylin-eosin, original magnification x100 and x200. C) *Helicobacter pylori* infection was observed in a large proportion of the study group. Whartin-Starry, x400

severe chronic active gastritis ($p<0.05$). Atrophy was also significantly associated with intestinal metaplasia and neuroendocrine cell hyperplasia ($p<0.001$). Approximately 6% ($n=55$) had atrophic gastritis with intestinal metaplasia, and 4% ($n=38$) had atrophic gastritis without intestinal metaplasia. Patients with atrophy and intestinal metaplasia were significantly older than those without atrophy and intestinal metaplasia ($p<0.001$; mean age: 47 and 46 vs 56 and 55, respectively). More than half of the patients were infected with *H. pylori* (57%; $n=542$) (Figure 1C), and *H. pylori* positivity was associated with the presence of chronic gastritis, chronic active gastritis, LH, and regenerative mucosal changes ($p<0.001$). The density of *H. pylori* and lymphoid aggregates decreased significantly with age ($p<0.001$). The severity of chronic gastritis and chronic active gastritis were also significantly correlated with *H. pylori* density ($p<0.001$). In contrast, erosion, atrophy, and neuroendocrine cell hyperplasia were less common in patients with *H. pylori* gastritis ($p<0.05$). Sixty-eight patients (7%) with *H. pylori* infection showed intestinal metaplasia without mucosal atrophy. Only 45 (8%) of *H. pylori*-positive patients had atrophic gastritis.

The most common non-gastritis histopathologic diagnosis was gastric carcinoma (2.5%; $n=24$), followed by polypoid lesions (1.6%; $n=16$) (Table 2). Patients with malignant tumors, dysplasia, and polypoid lesions were significantly older than those with gastritis and/or erosion/ulceration (median: 71.5 ± 15.5 vs 47 ± 17 ; $p<0.001$), but there was no significant association between gender and lesion type, although polypoid lesions tended to be more common among women (Table 3).

Discussion

In this study, we observed that the majority of patients (92%) had chronic gastric inflammation, and more than half (57%) had chronic active gastritis. The relatively high proportion (57%) of patients with *H. pylori* infection within the study group and the significant association of *H. pylori* positivity with the presence of both chronic and chronic active inflammation suggest that *H. pylori* infection is a major cause of gastritis. On the other hand, the *H. pylori* positivity rate was strikingly lower than previously reported in southeastern Anatolia (57% vs 89%) (8), despite the fact that our study group consisted of symptomatic patients. Moreover, of the 360 *H. pylori*-negative patients, 334 had chronic and 138 had chronic active gastritis, indicating that gastritis is common in the region regardless of *H. pylori* status. Recently, in a study of patients with chronic gastritis, barbecue and spicy foods were associated with dyspeptic symptoms (9). While *H. pylori* acts both as a cause and an exacerbating factor for gastritis, the regional habit of consuming mainly roasted hot peppers and spicy food is probably another major source of gastric mucosal irritation and inflammation. However, data on the effect of capsaicin (i.e., the active ingredient of pepper) on the gastric mucosa is controversial. It was reported to induce acute erosive gastritis in 1970s (10), but recent studies have shown that capsaicin inhibits gastric acid

output by vagal inhibition (11), inhibits in vitro proliferation of *H. pylori*, and decreases gastric neutrophilic infiltration (12) in animal studies. Mózsi et al. (13) have demonstrated that the effects of capsaicin on the gastric mucosa is dose- and time-dependent: while a small dose of capsaicin inhibits gastric acid secretion, a high dose causes hyperacidity and associated mucosal damage. It has been suggested that capsaicin-sensitive afferent nerves are involved in the course of gastritis, regardless of *H. pylori* infection (14) and that these nerves may exhibit both pro- and anti-inflammatory effects (15). The dose-dependent nature of the relationship explains the conflicting results reported in the literature. We also found a significant association between erosive gastritis and *H. pylori* negativity, which may be attributable to the hyperacidity-inducing effects of high-dose capsaicin, in this case, consuming large amounts of

Table 2. Histopathologic characteristics

Frequency of inflammatory lesions	
Chronic gastritis	92% (n=875)
Mild	24% (n=229)
Moderate	38% (n=361)
Severe	30% (n=285)
Chronic active gastritis	57% (n=537)
Mild	22% (n=205)
Moderate	23% (n=220)
Severe	12% (n=112)
Gastric ulcer	2% (n=19)
Erosion	1% (n=10)
Frequency of <i>Helicobacter pylori</i> infection 57% (n=542)	
Frequency of inflammation associated mucosal changes	
Regenerative/reactive changes	27% (n=254)
Foveolar hyperplasia	8% (n=77)
Atrophy	10% (n=93)
Intestinal metaplasia	19% (n=176)
Neuroendocrine cell hyperplasia	4.5% (n=42)
Frequency of dysplastic/neoplastic lesions 3.1% (n=30)	
Low-grade dysplasia	0.2% (n=2)
High-grade dysplasia	0.4% (n=4)
Adenocarcinoma	1.6% (n=15)
Diffuse type (signet ring cell) carcinoma	0.6% (n=6)
Neuroendocrine carcinoma	0.1% (n=1)
Mucinous carcinoma	0.1% (n=1)
Melanoma	0.1% (n=1)
Frequency of polypoid lesions 1.6% (n=16)	
Hyperplastic polyp/polypoid foveolar hyperplasia	1.2% (n=11)
Fundic gland polyp	0.4% (n=4)
Adenomatous polyp	0.1% (n=1)

Table 3. Association of histopathologic diagnosis with age and gender

	Gastritis/erosion/ulceration	Reflux gastropathy	Polyps	Dysplasia	Malignant	Normal	p
Gender (female/male ratio)	1.16	1 female	2.75	0.5	0.5	1.18	0.146
Mean/median age \pm SD	48/46 \pm 17	n=1; age: 49	66/65 \pm 14	66/67 \pm 12	68/72 \pm 16	52/51 \pm 12	<0.001

SD: Standard deviation

spicy food. However, given that this is a cross-sectional, retrospective study, it is not possible to determine a precise causal relationship between diet and chronic gastritis. A prospective study design may be helpful in this regard. Of note, a similar dose-dependent effect of capsaicin has also been documented for gastric cancer formation (4).

The significant association between the severity of neutrophilic activity and reactive changes such as regenerative mucosal changes and foveolar hyperplasia is not surprising. It is somewhat unexpected that atrophy and neuroendocrine cell hyperplasia were less common in patients with *H. pylori* gastritis, considering that long-term and/or persistent *H. pylori* infection is known to cause atrophic gastritis. This finding indicates that the predominant mechanisms for atrophic gastritis in the study group are autoimmune pathway and environmental factors, including a high-fat diet (16) and high salt intake (17), although the evaluation of multifocal atrophic gastritis was limited due to the small number of patients with concurrent antrum and corpus biopsies. Patients with atrophy and intestinal metaplasia were significantly older, consistent with previous studies reporting that atrophic gastritis is more common in older age groups (17,18), which most likely results from decreasing repair capacity with aging (19). The decreasing tissue repair capacity with aging may also be responsible for the increased frequency of occurrence of gastric ulcer in older patients. A decrease in gastric mucosal surface hydrophobicity with age has also been suggested to contribute to gastric ulcer formation in older individuals (20).

The association between age and inflammatory activity was another noteworthy finding. The severity of chronic inflammation, density of *H. pylori* positivity, and associated lymphoid aggregates decreased significantly with age. Other than the possibility of earlier *H. pylori* eradication, this may be a result of a reduction in T-cell response with aging (21) and the accompanying decrease in B-cell stimulation within the mucosa-associated lymphoid tissue. Therefore, it would be reasonable to claim that while the chronic inflammatory response decreases with age, acute responses such as ulceration become predominant in older individuals due to impaired mucosal defense mechanisms.

Gastric cancer is the fifth most common type of cancer in Turkey (22). The frequency of gastric malignancy in our study group was 2.5%. The tumor type was adenocarcinoma in most of them, and the tumor was located in the antrum in 54%. Curiously, one patient was diagnosed with melanoma but unfortunately was lost to follow-up, and the distinction between primary and metastatic melanoma could not be made. Although rare, primary melanoma occurs in the stomach (23,24); however, detailed clinical and radiological examinations should be performed to rule out a primary tumor elsewhere in the body. We observed that patients with malignant tumors, dysplasia, and polypoid lesions were significantly older than those with inflammation. This may be attributed to longer exposure to carcinogens and the accumulation of mutations. Considering the two risk factors for gastric cancer, the high incidence of *H. pylori* infection and frequent intake of spicy foods, closer monitoring may be beneficial to detect gastric cancer cases at early stages in this region. It should also be noted here that preinvasive neoplastic and dysplastic lesions may also occur, especially due to *H. pylori* gastritis. While the frequency of dysplasia was <1% in our series,

the frequency of high-grade dysplasia (0.4%) was slightly higher than the annual incidence of high-grade dysplasia (0.18%) recently reported from a different geographic region of Turkey (25), suggesting that tight monitoring may be an efficient method of following up with individuals in higher-risk regions.

Conclusion

H. pylori infection and frequent spicy food intake seem to be the key factors in the development of gastritis among inhabitants of Southeastern Anatolia. However, prospective epidemiological studies are needed to better demonstrate the causal effect of dietary factors in the pathogenesis of gastritis in patients with dyspeptic symptoms in this region.

Ethics

Ethics Committee Approval: The study protocol was approved by the Adiyaman University Faculty of Medicine Institutional Ethics Committee (approval no: 2017/9-8, date: 19.12.2017).

Informed Consent: Informed consent was not sought due to the retrospective nature of the study.

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