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Etiological factors of duodenal and gastric ulcers

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Background/aims: *We aimed to determine the etiology of patients with duodenal and gastric ulcers.* ***Methods:*** *140 patients diagnosed with peptic ulcer between April 2002-2009 were enrolled in this prospective study. Two biopsy specimens were collected from the antrum and corpus for histology and one for rapid urease testing, and stool samples were analyzed for Helicobacter pylori antigen. Serum calcium and gastrin levels were also analyzed.* ***Results:*** *82 (58%) patients were male, with a median age of 47.70±15.03 years (range: 16-92). The ulcer was located in the duodenum in 96 patients, stomach in 40, and both duodenum and stomach in 4. The rates of patients positive for Helicobacter pylori antigen in stool, positive in urease testing and positive for Helicobacter pylori presence in antral and corpus samples were 48%, 52%, 67%, and 60%, respectively. 107 (76%) patients were positive for Helicobacter pylori in one of the test methods. 64 (46%) patients had a history of nonsteroidal antiinflammatory drug use within the last month. Mean levels of calcium and gastrin were 9.29±0.40 (7.90-10.20) and 73.96±89.88 (12.86-562.50), respectively. Gastrin level was correlated to inflammatory activity ($p<0.05$). 19 (13.6%) of the patients were negative for Helicobacter pylori, nonsteroidal antiinflammatory drug use and hypersecretory illness, and were classified as idiopathic.* ***Conclusions:*** *The most common cause of duodenal and gastric ulcer was Helicobacter pylori, and it was responsible for three-fourths of the cases. About half of the patients had a history of nonsteroidal antiinflammatory drug use, and nonsteroidal antiinflammatory drug and Helicobacter pylori were both responsible for the ulcer in three-fourths of these patients. In about one-tenth of the patients, nonsteroidal antiinflammatory drug use was the cause of ulcer alone, and about one-tenth of the ulcers were classified as idiopathic.*

Key words: Peptic ulcer, gastric ulcer, duodenal ulcer, etiology

Duodenal ve gastrik ülserin etyolojisi

Amaç: *Duodenum ve mide ülserli hastaların etyolojisini tesbit etmek.* ***Yöntem:*** *Nisan 2002-2009 tarihleri arasında Endoskopi Ünitesine gastroskopi için başvuran ve peptik ülser saptanan 140 hasta prospektif olarak çalışmaya alındı. Hastalardan histolojik inceleme için antrumdan ve korpustan ikişer, üreaz için birer biyopsi alındı, gaitada Helikobakter pilori antijeni bakıldı. Her üç yöntemden herhangi birinde Helikobakter pilori pozitifliği varsa etyolojik neden olarak Helikobakter pilori kabul edildi. Histopatolojik olarak inflamasyon aktivitesi, intestinal metaplazi, atrofi ve Helikobakter pilori bakıldı. Serumda kalsiyum ve gastrin seviyeleri bakıldı.* ***Bulgular:*** *Hastaların 82'si (%58) erkek, yaş ortalması 47.70±15.03 yaş (dağılım 16-92), 62'si (%44) sigara, 18'i (%13) alkol kullanıyor idi. Ülser 96 hastada duodenumda, 40 hastada midede, 4 hastada mide ve duodenumda yerleşmiş idi. Gaitada Helikobakter pilori antijen pozitifliği, üreaz pozitifliği, antrumda ve korpusta histolojik Helikobakter pilori varlığı sırasıyla; %48, %52, %67 ve %60 idi. Helikobakter pilori 107 hastada (%76) yöntemlerden herhangi birinde pozitif idi. Son 1 ay içerisinde nonsteroid antiinflamatuar ilaç kullanım hikayesi olan 64 hastanın (%46), 48'inde (%75) Helikobakter pilori pozitif, 16 hastada (25) negatif idi. Antrum biyopsilerinde inflamatuvar aktivite varlığı, atrofi, intestinal metaplazi sıklığı sırasıyla %65, %17.5, %11; korpusta ise %66, %6.5 ve %1.5 idi. Ortalama kalsiyum düzeyi 9.29±0.40 (7.90-10.20), gastrin düzeyi 73.96±89.88 (12.86-562.50) idi. Gastrin düzeyi yüksek olan hastaların histolojik incelemelerinde hipersekretuar durum tesbit edilmedi. Gastrin yüksekliği inflamasyon aktivitesi ile korele idi ($p<0.05$). 17 hastada Helikobakter pilori, nonsteroid antiinflamatuar ilaç kullanımı ve hipersekretuar hastalık tesbit edilmedi ve idiyopatik kabul edildi.* ***Sonuç:*** *Duodenum ve mide ülserinin en sık nedeni Helikobakter pilori olup hastaların dörtte üçünden sorumludur. Hastaların yaklaşık yarısında nonsteroid antiinflamatuar ilaç kullanımı öyküsü vardır ve bunların da dörtte üçünde ülserden nonsteroid antiinflamatuar ilaç ve Helikobakter pilori birlikte sorumludur. Hastaların yaklaşık onda birinde nonsteroid antiinflamatuar ilaç tek başına etyolojik neden olarak saptanırken, yaklaşık onda biri idiyopatiktir.*

Anahtar kelimeler: Peptik ülser, gastrik ülser, duodenal ülser, etyoloji

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INTRODUCTION

Peptic ulcer disease (PUD) had a tremendous effect on morbidity and mortality until the last decades of the 20th century. Development of new effective and potent acid suppressants and the discovery of *Helicobacter pylori (Hp)* are two important steps that caused a reduction in the prevalence of PU. With the discovery of *Hp*, causes, pathogenesis and treatment of PUD have been redefined in the last 25 years. However, this condition continues to be an important clinical issue because of common use of nonsteroidal antiinflammatory drugs (NSAIDs) and acetylsalicylic acid at low doses. The rare but increasingly problematic issue is *Hp*-negative and NSAID-negative ulcers (1). Despite progress in the diagnosis and treatment, PUD remains a common reason for hospitalization and operation (2).

Peptic ulcer disease (PUD) affects 10% of the world's population. *Hp* infection and the use of a NSAID are the principal factors associated with PUD (3). The declining global prevalence of PUD might be because of the decreasing prevalence of *Hp* infection (4). The decreasing prevalence of *Hp* could lead to a relative increase in the number of patients with this NSAID-associated and idiopathic PUD (5). Another view is that incidence of PUs decreased and an increasing proportion was related to NSAID and the mortality was high (6). It is also known that the incidence of idiopathic PUD has increased (7,8).

Hp infection causes both gastric and duodenal ulcers. Current data show that *Hp* infection plays a major role in PUD and non-ulcer dyspepsia (9,10). Apart from these diseases, *Hp* is thought to play a role in the etiology of atrophic gastritis, gastric adenocarcinoma and lymphoma. In our country, *Hp* prevalence remains an important health problem (11).

The aim of this study was to determine the etiology of patients with duodenal and gastric ulcers.

MATERIALS AND METHODS

Between April 2002 and April 2009, 140 patients who referred to our endoscopy laboratory with upper gastrointestinal system bleeding or dyspeptic complaints for gastroscopy and were diagnosed with PU (duodenal and/or gastric) were enrolled in this prospective study. Approximately 14,970 gastroscopies were taken; 890 (5.9%) gastric ulcers and 1261 (8.4%) duodenal ulcers were observed in the endoscopy unit of our hospital between 2002 and 2009. Before the procedure, medical history, cigarette smoking and alcohol consumption and NSAID and acetylsalicylic acid use within the last month were queried. The last 4 weeks and 2 times more than the presence of drug use NSAIDs have been considered as a cause of ulcers. Patients with a history of gastric operation, with malignant ulcer or another malignant disease and those unwilling to participate in the study were excluded.

Ulcer lesions are described as larger than 5 mm, extending from the lamina propria and with exudation. Two biopsy specimens were collected from the antrum and corpus for histology and one for rapid urease testing, and stool samples were analyzed for *Hp* antigen using Laboquick *Hp* antigen test kit. A patient was classified as being *Hp*-positive if any of the three test methods was positive. NSAID and/or acetylsalicylic acid use within the last month was associated with ulcer, if any. Inflammatory activity, intestinal metaplasia, atrophy, and *Hp* were evaluated in the histopathological examination, according to the updated Sydney system (12). Serum calcium and gastrin levels were also analyzed. Serum gastrin levels were measured using radioimmunoassay (RIA) method, MP-RIA test kit.

The Statistical Package for the Social Sciences (SPSS) 13.0 statistical program was used for statistical assessments. Mean ± standard deviation (SD) or median were used for quantitative variables. For independent group comparisons, intergroup variations were analyzed with non- parametrical Mann–Whitney U test. Intergroup variations were evaluated using Wilcoxon test (for dependent group comparison). Correlation analyses were performed using Pearson and Spearman correlation tests. Results with p value less than 0.05 were accepted as statistically significant.

RESULTS

Eighty-two (58%) of the patients were male and 58 (42%) were female. The mean age was 47.70 ± 15.03 years (range: 16-92). Sixty-two (44%) of the patients were smoking and 18 (13%) were drinking alcohol. One hundred and thirty-two (94%) of the patients were from urban areas, whereas 8 (6%) were from rural areas. Fourteen (10%) patients had a family history of PUD, whereas 4 (0.3%) had a family history of stomach cancer.

The ulcer was located in duodenum in 96 (69%),

stomach in 40 (28%), and both duodenum and stomach in 4 (3%) patients.

The rates of patients positive for *Hp* antigen in stool, positive in urease testing and positive for *Hp* presence in antral and corpus samples were 48%, 52%, 67%, and 60%, respectively (Table 1). One hundred and seven (76%) patients were positive for *Hp* in one of the test methods.

Among 64 (46%) patients with a history of NSAID use within the last one month, 48 (75%) were *Hp*-positive and 16 (25%) were negative (Table 2). The mean age of patients on NSAID therapy was higher compared to the non-users (51.26 ± 15.60, range: 21-92 vs. 45.32 ± 14.25, range: 16-80; p<0.05).

Incidences of inflammatory activity, atrophy and intestinal metaplasia were 65%, 17.5% and 11% in antral biopsies and 66%, 6.5% and 1.5% in corpus samples, respectively (Table 3).

Histopathological inflammatory activity was correlated with *Hp* (p<0.05). Mean levels of calcium and gastrin were 9.29 ± 0.40 (7.90-10.20) and 73.96 ± 89.88 (12.86-562.50), respectively. In patients with elevated gastrin levels, no hypersecretory condition was detected. Elevated levels of gastrin were correlated with inflammatory activity and presence of *Hp* (p<0.05).

Nineteen (13.6%) of the patients were negative for *Hp*, NSAID use and hypersecretory illness, and were classified as idiopathic. The mean age of these patients was 51.52 ± 13.88 years (range: 16-78). The ulcer was located in the duodenum of 13 (68%) and stomach of 6 (32%) patients. Eleven (58%) of the patients were male and 8% (42%) female. Nine (47%) of the patients were smoking and 3 (16%) were drinking alcohol. One patient had a family history of PUD and one had a family history of stomach cancer. The mean age of these patients was higher compared to patients with a known etiology (p<0.05); however, there were no statistical differences in terms of ulcer location, gender, smoking, alcohol consumption, and family history (p>0.5). The mean gastrin level of 60.07 ± 64.13 (12.86-183.61) was lower compared to the patients with a known etiology (p<0.05), whereas calcium levels of 9.33 ± 0.6 (7.9-10.2) were similar (p>0.5).

Table 1. Incidence of Helicobacter pylori (*H. pylori*) in peptic ulcer using various methods

Stool sample positive for *H. pylori*	48%
Positive rapid urease testing	52%
H. pylori-positive antral histology	67%
H. pylori-positive corpus histology	60%
H. pylori-positive with any method	76%

Table 2. Peptic ulcer disease (PUD) etiology

Etiology	Number of patients (n)	Percentage (%)
H. pylori positive PUD	107	76%
NSAID use	64	(46%)
NSAID+*H. pylori*-positive	48	(75%)
NSAID+*H. pylori*-negative	16	(25%)
Idiopathic PUD	17	12%

Table 3. Histology findings of the biopsy samples: according to the updated Sydney system (12)

	Antrum	Corpus
Inflammatory activity	65%	66%
Atrophy	17.5%	6.5%
Intestinal metaplasia	11%	1.5%
H. *pylori* incidence	67%	60%

DISCUSSION

In our study, the most common cause of duodenal and gastric ulcer was *Hp*, which was responsible for three-fourths of the cases. About half of the patients had a history of NSAID use, and NSAID and *Hp* were both responsible for the ulcer in three-fourths of these patients. In about one-tenth of the patients, NSAID use was the cause of ulcer alone, and about one-tenth of the ulcers were classified as idiopathic.

Fifty-four (19%) of 277 consecutive patients had evidence of PUD (34 gastric ulcer, 14 duodenal ulcer and 6 both gastric and duodenal ulcer) in a similar study where demographic and endoscopic characteristics of patients with *Hp*-positive and -negative chronic PUD were evaluated (13). The most common finding in that study was gastric ulcer, whereas in our study, among 140 patients with PUD, 96 (69%) had duodenal ulcer, 40 (28%) had gastric ulcer, and 4 (3%) had both duodenal and gastric ulcer. These variations may be associated with the regional characteristics, lower number of patients evaluated in the other study and etiological differences.

Hp infection and the use of NSAIDs are the principal factors associated with PUD (3). Similarly, the etiologic factor in 88% of patients in our study was *Hp* and/or NSAID use.

While incidence of PUD associated with *Hp* infection is decreasing, especially in western countries (5,7,8), in our country, the most common cause is *Hp* (76%). It may be associated with the fact that *Hp* prevalence remains an important health problem in our country, and prevalence in the community is very high. In a study performed in our country with 9,239 patients who underwent gastrointestinal endoscopy, *Hp* incidence was 41.44% using the CLO test (11).

In a study evaluating the demographic and endoscopic characteristics of PUD, urease, culture, histology, serum anti-*Hp* IgG antibody, demographic data, and NSAID use within the last three months were assessed. Fifty-six percent of patients were *Hp*-positive and 22% were using NSAID (70% were *Hp*-positive) (13). In our study, *Hp* was evaluated using urease testing, *Hp* antigen in stool and histology, and the rates of patients who were *Hp*-positive and had used NSAID within the last month were higher (76% and 46%, respectively). Similarly, some patients using NSAID (75%) were also *Hp*- positive.

Hp induces chronic inflammation of the gastric mucosa, but only a proportion of infected individuals develops PUD or gastric carcinoma. The reasons underlying these observations include differences in bacterial pathogenicity as well as in host susceptibility (14). Meta-analyses have shown that *Hp* eradication therapy was effective for healing and prevention of recurrence of PUs in *Hp*-positive patients and that treatment of *Hp* infection was more effective than antisecretory non-eradicating therapy (with or without long-term maintenance therapy) in preventing recurrent bleeding (15). *Hp* eradication has been associated with decreased risk of gastric cancer in patients with PUD (16). In our study, *Hp* was also correlated with inflammatory activity. When it is considered that the *Hp*-associated PUD is a common disease in our country, more importance should be given to eradication therapy, both for effective treatment of PUD and for cancer prophylaxis.

Nonsteroidal antiinflammatory drugs (NSAIDs) have known detrimental side effects on the gastrointestinal system. The risk is increased with older age and history of PUD. *Hp* infection and cardioprotective acetylsalicylic acid have additive risks in the presence of NSAID use (17). The development of PUD was observed earlier in the combined *Hp* and NSAID group than in patients with only NSAID use, which suggests a synergistic effect between the two risks factors in the development of PUD (3). In our study, 75% of patients with a history of NSAID therapy were *Hp*-positive. This finding suggests that *Hp* and NSAID usage, when together, increase the risk of PUD.

Apart from *Hp* and NSAID, risk factors such as smoking, alcohol consumption, age, and male gender were reported as contributing to gastric and duodenal ulcer development (18-21). In our study, patients who supported these findings were of middle or older age and 58% of them were male. Almost half of the patients (44%) were smokers and 13% had alcohol intake.

The rate of patients classified as idiopathic (*Hp*-negative, NSAID-negative) was reported as 4%-20% (5,8,17). Among 140 patients, 19 (13%) were *Hp*- and NSAID- negative. Idiopathic ulcer was reported among younger patients in one study (13), whereas the 19 patients classified as idiopathic in our study were older compared to patients with a known etiology.

Apart from *Hp*, poor socioeconomic status has been reported as an important risk factor for PUD infection, while genetic factors do not influence the risk of PUD (22). Although the socioeconomic status of the patients enrolled in our study was not investigated in detail, 132 (94%) of the patients were from urban regions, while 8 (6%) were from rural areas, and 14 (10%) had a history of ulcer.

In conclusion, the most common cause of duodenal and gastric ulcer is *Hp*, and it was responsible for three-fourths of the cases in this study. About half of the patients had a history of NSAID use, and NSAID and *Hp* together were responsible for the ulcer in three-fourths of these patients. In one-tenth of the patients, NSAID use was the cause of ulcer alone, and about one-tenth of the ulcers were classified as idiopathic.

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