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The Etiological Factors of Duodenal and Gastric Ulcers

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1. Introduction

1.1 Background

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* (*H. pylori*) are two important steps that caused a reduction in the prevalence of peptic ulcer. With the discovery of *H. pylori*, causes, pathogenesis and treatment of PUD have been defined again in the last 25 years. However, this condition continues to be an important clinical issue because of common use of nonsteroidal anti-inflammatory drugs (NSAID) and acetylsalicylic acid at low doses. The rare but increasingly problematic issue is *H. pylori*-negative and NSAID-negative ulcers (1). Despite progress in diagnosis and treatment, peptic ulcer disease (PUD) remains a common reason for hospitalization and operation (2).

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

H. pylori infection causes both gastric and duodenal ulcers (35-27). Current data shows that *H. pylori* infection plays a major role in peptic ulcer disease and non-ulcer dyspepsia (9,10). Apart from these diseases, *H. pylori* are thought to play a role in the etiology of atrophic gastritis, gastric adenocarcinoma and lymphoma. In our country, *H. pylori* prevalence remains an important health problem (11).

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

2. Materials-methods

Between April 2002 and April 2009, 140 patients who referred to our endoscopy laboratory with dyspeptic complaints for gastroscopy and diagnosed with peptic ulcer (duodenal and/or gastric) were enrolled to this prospective study. Before the procedure, medical history, cigarette smoking and alcohol consumption and nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid use within the last month were queried. Patients with a history of gastric operation, with malign ulcer or another malign disease and who were not willing to participate the study were excluded.

Two biopsy specimens were collected from antrum and corpus for histology and one for rapid urease testing and stool samples were analyzed for *Helicobacter pylori* (H pylori) antigen using Laboquick H pylori antigen test kit. A patient was classified as being H. pylori positive if any of the three test methods were positive. NSAID and/or acetylsalicylic acid use within the last month was associated with ulcer, if any. Inflammatory activity, intestinal metaplasia, atrophy and H. pylori were evaluated in histopathological examination. Serum calcium and gastrin levels were also analyzed.

SPSS 13.0 statistical program was used for statistical assessments. Mean \pm 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. Inter group 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.

3. Results

82 of the patients (58%) were male and 58% were female (42%). Mean age was 47.70 ± 15.03 (range 16-92). 62 of the patients (44%) were smoking and 18 (13%) were drinking alcohol. 132 of the patients (94%) were from urban whereas 8 (6%) were from rural areas. 14 patients (10%) had a family history of PUD, whereas 4 (0.3%) had a family history of stomach cancer. Ulcer was located in duodenum in 96 patients (69%), in stomach in 40 patients (28%), and both in duodenum and stomach in 4 patients (3%).

Rate of patients tested positive for H pylori antigen in stool, positive in urease testing and tested positive for H. pylory presence in antral and corpus samples were 48%, 52%, 67% and 60% respectively (see Table 1). 107 patients (76%) were positive for H. pylori in one of the test methods.

Method	Incidence
Stool sample for H pylori positive	48%
Rapid urease testing positive	52%
H pylori positive antral histology	67%
H pylori positive corpus histology	60%
H pylori positive with any method	76%

Table 1. Incidence of H. pylori in peptic ulcer using various methods.

Among 64 patients (46%) with a story of nonsteroidal antienflammatory drug (NSAID) use within the last 1 month, 48 (75%) were Hp positive and 16 were (25%) negative (see Table 2).

Mean age of patients on NSAID therapy higher 51.26 ± 15.60 (range 21-92) compared to the non-users 45.32 ± 14.25 (range 16-80) ($p<0.05$).

H pylori positive PUD	107	76%
NSAID use	64	(46%)
NSAID+H pylori positive	48	(75%)
NSAID+ H pylori negatifliği	16	12% (25%)
Idiopathic PUD	17	12%

Table 2. Peptic ulcer (PUD) etiology

Incidence 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 (see Table 2).

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

Table 3. Histology findings of the biopsy samples

Histopathologically inflammatory activity was correlated with H. pylori ($p<0.05$). 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 H. pylori ($p<0.05$).

19 of patients (13.6%) were negative for H pylori, NSAID use and hypersecretory illness and classified as idiopathic. Mean age of these patients were 51.52 ± 13.88 (range 16-78). Ulcer was located in the duodenum of 13 patients (68%) and in stomach of 6 patients (32%). 11 of the patients (58%) were male and 8% were female (42%). 9 of the patients (47%) were smoking and 3 (16%) were drinking alcohol. 1 patient had a family history of PUD and 1 had a family history of stomach cancer. 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 ($p>0.5$). 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 ($p>0.5$).

4. Discussion

54 (19%) of 277 consecutive patients had evidence of peptic ulcer disease (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 Helicobacter pylori positive and negative chronic peptic ulcer disease were evaluated (12). The most common finding in this study was gastric ulcer whereas in our study, among 140 patients with PUD 96 (69%) had duodenal ulcer, 40 had (28%) gastric ulcer and 4 had (3%) both duodenal and gastric

ulcer in our study. These variations may be associated with the regional characteristics, lower number of patients evaluated in the other study and etiological differences.

Helicobacter pylori infection and the use of a nonsteroidal anti-inflammatory drug (NSAID) are the principal factors associated with PUD (3). Similarly, etiologic factor in 88% of patients in our study was *H. pylori* and/or NSAID use.

While incidence of PUD associated with *H. pylori* infection is decreasing especially in western countries (5,7,8), in our country most common cause is *H. pylori* (76%). It may be associated with the fact that *H. pylori* 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 9239 patients who underwent gastrointestinal endoscopy, *H. pylori* incidence was 41.44% using the CLO test (11).

In a study where demographic and endoscopic characteristics of peptic ulcer were evaluated, urease, culture, histology and serum anti-*H. pylori* IgG antibody were evaluated in patients and demographic data as well as NSAID use within the last 3 months were assessed. 56% of patients were *H. pylori* positive and 22% were using NSAIDs (70% were *H. pylori* positive) (12). In our study *H. pylori* was evaluated using urease testing, *H. pylori* antigen in stool and histology and rate of patients who are *H. pylori* positive and using NSAIDs within the last month were higher (76% and 46% respectively). Similarly, some patients using NSAID (75%) were also *H. pylori* positive.

H. pylori induces chronic inflammation of the gastric mucosa, but only a proportion of infected individuals develop peptic ulcer disease or gastric carcinoma. Reasons underlying these observations include differences in bacterial pathogenicity as well as in host susceptibility (13). Meta-analyses showed that *Helicobacter pylori* eradication therapy was effective for healing and prevention of recurrence of peptic ulcers in *H. pylori*-positive patients and that treatment of *H. pylori* infection was more effective than antisecretory non-eradicating therapy (with or without long-term maintenance therapy) in preventing recurrent bleeding (14). *H. pylori* eradication has been associated with decreased risk of gastric cancer in patients with peptic ulcer diseases (15). In our study, *H. pylori* were also correlated with inflammatory activity. When it is considered that the *H. pylori* associated PUD is a common disease in our country, we should give more importance to eradication therapy both for effective treatment of PUD and for cancer prophylaxis.

NSAIDs have known detrimental side effects on the gastrointestinal system. The risk is increased with older age and history of PUD. *Helicobacter pylori* infection and cardioprotective acetylsalicylic acid have additive risks in the presence of NSAID use (16). The development of PUD was observed earlier in the combined *H. pylori* and NSAID group than in patients with only NSAID use and this suggests a synergic effect between the two risk factors in the development of PUD (3). In our study, 75% of patients with history of NSAID therapy were *H. pylori* positive. This finding suggests that *H. pylori* and NSAID usage, when together, increases the risk of PUD.

Apart from *H. pylori* and NSAID, risk factors such as smoking, alcohol intake, age, and male gender were reported as contributing to the gastric and duodenal ulcer development (17-20). In our study, patients who are supporting these findings were at middle or older age and 58% of them were male. Almost half of the patients (44%) were smokers and 13% were drinking alcohol.

Rate of patients classified as idiopathic (*H. pylori* negative, NSAID negative) were reported between 4 and 20% (5, 8, 17). Among 140 patients 19 were (13%) *H. pylori* and NSAID

negative. Idiopathic ulcer was reported among younger patients in a study (12) where as 19 patients classified as idiopathic in our study were older compared to patients with a known etiology.

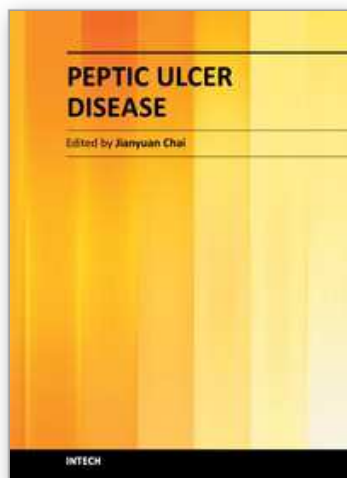
Apart from *H. pylori*, poor socio-economic status has been reported as an important risk factor for PUD infection while genetic factors do not influence the risk of PUD (21). Although the socio-economic status of the patients enrolled in our study has not been investigated in detail, 132 of the patients (94%) were from the urban regions while 8 (6%) were from the rural area and 14 (10%) had a history of ulcer.

As a consequence, most common cause of duodenal and gastric ulcer is *H. pylori* and is responsible for three-fourths of the cases. About half of the patients had a history of NSAID use and NSAID and *H. pylori* are both 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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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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