

H. pylori infection and other risk factors associated with peptic ulcers in Turkish patients: A retrospective study

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Abstract

AIM: To identify and evaluate the relative impact of *H. pylori* infection and other risk factors on the occurrence of gastric ulcer (GU), duodenal ulcer (DU) and gastritis in Turkish patients.

METHODS: A total of 4471 patients (48.3% female) out of 4863 attended the Samatya hospital in Istanbul (June 1999 - October 2003) were included. The records of *H. pylori* status (CLO-test), endoscopic findings of GU, DU and gastritis, personal habits (smoking, alcohol intake) and medication [non-steroidal anti-inflammatory drugs (NSAIDs), aspirin intake] were analyzed using multi-way frequency analysis.

RESULTS: We have found that GU in the presence of *H. pylori* had significant association with aspirin ($P = 0.0001$), alcohol ($P = 0.0090$) and NSAIDs ($P = 0.0372$). DU on the other hand had significant association with aspirin/ smoking/NSAIDs ($P = 0.0259$), aspirin/alcohol ($P = 0.0002$) and aspirin/smoking ($P = 0.0233$), also in the presence of *H. pylori*. In the absence of *H. pylori* GU had significant association with alcohol/NSAIDs ($P = 0.0431$), and NSAIDs ($P = 0.0436$). While DU in the absence of *H. pylori* had significant association with smoking/alcohol/ NSAIDs ($P = 0.0013$), aspirin/NSAIDs ($P = 0.0334$), aspirin/alcohol ($P = 0.0360$).

CONCLUSION: In the presence of *H. pylori*, aspirin, alcohol and NSAIDs intake act as an independent risk factors that had an augmenting impact on the occurrence of GU and only together on the occurrence of DU in Turkish patients.

INTRODUCTION

Among the variety of human infections, *H. pylori* infections are one of the most common infections. It is generally accepted that several factors are involved in the etiology of peptic ulcer disease (PUD). Earlier studies, which were based only on interview survey and mailed questionnaire, correlated the effect of risk factors, but not *H. pylori* with the occurrence of PUD. In one study conducted in the United States, increasing age, lower income, educational status and smoking were the main risk factors associated with PUD^[1]. Similarly in Norway, age and smoking were the important factors^[2]. However, Aldoori *et al*^[3] did not find smoking to be a substantial risk factor of duodenal ulcer.

Since there is variability in the geographic distribution of *H. pylori* infections, this might suggest that risk factors involved in the occurrence of peptic ulcer also varies among different populations^[4]. In several clinical and epidemiological studies risk factors for PUD were attributed to *H. pylori* infection, non-steroidal anti-inflammatory drugs (NSAIDs) intake and smoking. In a recent study^[5], tobacco smoking and *H. pylori* infection were found to be the main risk factors for PUD in Danish adults. Kurata and Nogawa^[6] in a meta-analysis report showed that 89%-95% of PUD might be attributed to NSAIDs use, *H. pylori* infection and cigarette smoking.

So far few population-based studies that correlate the effect of *H. pylori* with other PUD risk factors are being reported. Also the incidence and risk factors for PUD in Turkey have not been well defined. Our objectives were to identify and evaluate the relative impact of each single risk factor, smoking, alcohol, NSAIDs or aspirin intake (in the presence or absence of *H. pylori* infection) on the occurrence of gastric ulcer (GU) and duodenal ulcer (DU) in Turkish patients.

MATERIALS AND METHODS

Patients

Four thousand four hundred and seventy one patients out of 4863 (83% were out-patients) who have attended the endoscopy unit at the Samatya Hospital in Istanbul during the period from June 1999 to October 2003 were included in this study. The mean age \pm SD was 48.2 ± 14.7 years with a range of 16-83 years (48.3% female). A questionnaire form was filled out for each patient before endoscopy and the data were saved. The main complaints documents by patients were dyspepsia, abdominal pain, vomiting, nausea and acidity. Patients, who were on medications (antibiotics, proton pump inhibitors) for the last 2 mo, follow up patients and those who had both DU and GU were excluded. Only the records of patients who under went upper gastroendoscopy for the evaluation of gastroduodenal changes were included and from those, antral biopsies were taken for CLO-test. The records for the assessment of *H pylori* infections status (CLO-test), the endoscopic findings of GU, DU and gastritis, personal habits of smoking (> 10 cigarettes/d), alcohol intake [> 3 alcoholic (no wine) drinks/d] and medication (NSAIDs, aspirin intake) were analyzed.

Statistical analysis

Relationships between two or more discrete variables are studied through multi-way frequency analysis or an extension of it called log-linear analysis^[7,8]. It is an extension of the familiar chi-square test for independence in two-way contingency tables. A log-linear model is developed where an additive regression-type equation is written for (the log of) expected frequency as a function of the effects in the design. The procedure is similar to multiple-regression where a predicted dependent variable is obtained by combining the effects of several independent variables. A full (saturated) model includes all possible effects in a multi-way frequency analysis. For saturated models, one can request either parameter estimates or tests of partial association. We have considered the partial associations instead of a parameter estimates as an alternative way of testing effects. The overall goodness-of-fit of a model is assessed by comparing the expected frequencies and the observed cell frequencies for each model. The Pearson Chi-square statistic or the likelihood ratio (G^2) can be used to test a models fit. However, the G^2 is more commonly used because it is the statistic that is minimized in maximum likelihood estimation and can be partitioned uniquely for more powerful test of conditional independence in multi-way tables.

RESULTS

H pylori infection detected by the CLO-test was positive in 2805 (62.7%) out of 4471 patients. The prevalence of infection and the incidence of peptic ulcers and gastritis among male and female patients were shown in Table 1. The prevalence of *H pylori* infection was significantly higher in DU patients than those in GU (74.8% vs 62.8%), but not gastritis patients. Male patients (65.6%) had significantly higher incidence of peptic ulcers than female

Table 1 The prevalence of *H pylori*, social habits (smoking, alcohol intake) and medication (NSAIDs, aspirin intake) among peptic ulcers and gastritis patients *n* (%)

Disease	<i>H pylori</i> (+)	Smoking	Alcohol	NSAID	Aspirin
DU (<i>n</i> = 826)	618 (74.8)	237 (28.7)	68 (8.2)	211 (25.5)	45 (5.4)
M = 541	391 (72.3)	191 (35.3)	64 (11.8)	138 (25.5)	36 (6.7)
F = 285	227 (79.6)	46 (16.1)	4 (1.4)	73 (25.6)	9 (3.2)
GU (<i>n</i> = 207)	130 (62.8)	57 (27.5)	19 (9.1)	54 (26.0)	19 (9.1)
M = 137	85 (62.0)	45 (32.8)	19 (13.9)	28 (20.4)	16 (11.7)
F = 70	45 (64.3)	12 (17.1)	0 (0)	26 (37.1)	3 (4.3)
G (<i>n</i> = 3160)	1896 (70.7)	626 (19.8)	159 (5.0)	687 (21.7)	79 (2.5)
M = 1351	807 (59.7)	373 (27.6)	141 (10.4)	264 (19.5)	43 (3.2)
F = 1809	227 (12.5)	253 (14.0)	18 (1.0)	423 (23.4)	36 (2.0)
Total (<i>n</i> = 4193)	2644 (63.1)	920 (21.9)	246 (5.9)	952 (22.7)	143 (3.4)
M = 2029	1283 (63.2)	609 (30.0)	224 (11.0)	430 (21.2)	95 (4.7)
F = 2164	499 (23.0)	311 (14.4)	22 (1.0)	522 (24.1)	48 (2.2)

NSAID: non-steroidal anti-inflammatory drug; *n*: number tested; DU: duodenal ulcer; GU: gastric ulcer; G: gastritis; M: male; F: female.

patients (34.4%). The frequencies of social habits (smoking, alcohol intake) and medication (NSAIDs and aspirin intake) among male and female patients were also shown in Table 1. Smoking and alcohol intake were significantly higher among male patients than females (34.8% vs 15.7% and 12.2% vs 1.1% respectively) and similarly for aspirin (7.6% vs 3.3%), but not for NSAIDs intake (24.5% vs 27.8%). No significant differences were found in the above risk factors among the DU and GU patients.

The association of GU, DU or gastritis with the risk factors smoking, alcohol, NSAIDs and aspirin intake in the presence or absence of *H pylori* was shown in Table 2. We have found that GU in the presence of *H pylori* had significant association with aspirin ($P = 0.0001$), alcohol ($P = 0.0090$) and NSAIDs ($P = 0.0372$). DU on the other hand had significant association with aspirin/smoking/NSAIDs ($P = 0.0259$), aspirin/alcohol ($P = 0.0002$) and aspirin/smoking ($P = 0.0233$), also in the presence of *H pylori*. In the absence of *H pylori* GU had significant association with alcohol/NSAIDs ($P = 0.0431$), and NSAIDs ($P = 0.0436$). While DU in the absence of *H pylori* had significant association with smoking/alcohol/NSAIDs ($P = 0.0013$), aspirin/NSAIDs ($P = 0.0334$), aspirin/alcohol ($P = 0.0360$).

The distribution pattern of the social habits (smoking and alcohol) and medication (NSAIDs and aspirin intake) among different age groups (teens, twenties, and so on) in this study was as follows: There was an increase in the pattern of intake of the above factors with increased age among male patients, but smoking and alcohol intake habits appeared to decline with increasing age (data not shown).

DISCUSSION

H pylori infection is known to be very common worldwide. However, only a small percentages of the infected population develop PUD. Several risk factors such as smoking, alcohol, NSAIDs and aspirin intake are shown to play a role in the disease outcome. The characterization

Table 2 The partial association of the risk factors: smoking, alcohol, NSAIDs and aspirin intake with *H pylori* (+) or (-) peptic ulcers and gastritis

GU (risk factor)	G ²	P-value	DU (risk factor)	G ²	P	Gastritis (risk factor)	G ²	P
<i>Hp+</i> , aspirin	14.65	0.000	<i>Hp+</i> , aspirin, smoking, NSAID	4.96	0.026	<i>Hp+</i> , aspirin, smoking, NSAID	5.1	0.024
<i>Hp+</i> , alcohol	6.81	0.009	<i>Hp+</i> , aspirin, alcohol	13.53	0.000	<i>Hp+</i> , aspirin, alcohol	3.92	0.048
<i>Hp+</i> , NSAID	4.34	0.037	<i>Hp+</i> , aspirin, smoking	5.14	0.023	<i>Hp+</i> , smoking	4.7	0.03
<i>Hp-</i> , alcohol, NSAID	4.09	0.043	<i>Hp-</i> , smoking, alcohol, NSAID	10.31	0.001	<i>Hp+</i> , aspirin	5.81	0.016
<i>Hp-</i> , NSAID	4.07	0.044	<i>Hp-</i> , aspirin, NSAID	4.53	0.033	<i>Hp-</i> , smoking, alcohol, NSAID	9.89	0.02
			<i>Hp-</i> , aspirin, alcohol	4.4	0.036	<i>Hp-</i> , aspirin	7.5	0.006

G²: likelihood ratio Chi-square ($\gamma = 1$); GU: gastric ulcer; DU: duodenal ulcer; *Hp*: *H pylori*; NSAID: non-steroidal anti-inflammatory drug.

of these factors according to their strength of effect was found to vary among different populations^[5,6]. Schlemper *et al*^[4] indicated that the proportion of ulcers that can be attributed to *H pylori* infection is likely to be higher in countries where *H pylori* infection is more common (e.g. Japan). They showed that *H pylori* had greater impact on ulcer morbidity in the Japanese than in the Dutch population.

According to clinical observations smokers were found more likely to develop ulcers that are difficult to heal and had higher incidence of relapses^[9]. Thus smoking although not an independent ulcerogen, may act by augmenting the harmful effects of *H pylori*, both by adversely affecting upper gastrointestinal mucosal protection and by increasing the risk of *H pylori* infection^[4,5,9]. It was reported that smoking more than 15 cigarettes per day compared with never smoking increased the risk of a perforated ulcer more than threefold^[10]. Recent studies also showed a significant modification effect between smoking and *H pylori* infection, and suggested that smoking only increases the risk of peptic ulcers in those who were infected with *H pylori*^[5,10]. Similarly Johnson *et al*^[2] reported that cigarette smoking is an important risk factor for peptic ulcer. In this study smoking showed no significant association with GU in the presence or absence of *H pylori* as it appeared for DU. This might be attributable to the fact that smoking had no direct contact with the gastrointestinal tissue and also to the high regenerating power of the gastric epithelium that renders such effect to be negligible. In addition, smoking did not act as an independent risk factor for DU, but did together with other risk factors. This further substantiates the fact that smoking had significant modifying and augmenting effect on such patients. Everhart, *et al*^[11] in a population-based sample of 42 392 individuals responded to questions regarding doctor-diagnosed ulcers concluded that smoking in the absence of *H pylori* might be a stronger risk factor for chronic ulcers than for new ulcers.

Bytzer and Teglbjaerg^[11] reported earlier that 12% of DU patients were *H pylori*-negative at entry and showed no differences according to *H pylori* status for a number of clinical and demographic characteristics. Such patients had a shorter history of ulcer symptoms and were more likely to be NSAIDs users. In another report^[12], it was shown that NSAIDs is also a risk factor for ulcer bleeding and that such risk was reduced in the presence of *H pylori*.

Sakamoto *et al*^[13] also showed that NSAIDs including loxoprofen increase the risk of upper gastrointestinal bleeding in Japan as in Western countries and found no evidence of biological interaction between NSAIDs and *H pylori* infection. Our results showed that NSAIDs intake as an independent risk factor or in association with other risk factors had significant association with GU in the presence or absence of *H pylori*. For DU, NSAIDs intake only with other risk factors showed a significant association despite the presence or absence of *H pylori*. Rosenstock *et al*^[5], however, found no association between NSAIDs use and PUD. It is well known that *H pylori* infection is highly associated with DU (95.7%) and GU (87%) and only 1.6% of DU and 4.1% of GU were not associated with either *H pylori* infection or NSAIDs use^[14]. Differences in the applied methods of analysis might be the reason for such controversy.

The use of aspirin is another risk factor for the development of peptic ulcers. Recently it was shown that low-dose aspirin was found commonly associated with ulcer bleeding^[12]. Aspirin intake in this study showed a similar association pattern to NSAIDs intake. Aspirin intake as an independent factor showed highly significant association with GU in the presence of *H pylori*. Aspirin also showed significant association with DU only when other risk factors are involved and regardless of the presence or absence of *H pylori*.

A possible explanation for the similarity in the association pattern between NSAIDs and aspirin intake might be the fact that although these agents makes direct contact with the gastric epithelium, its high regenerating power renders NSAIDs and aspirin alone to cause no severe damages in the absence of *H pylori*. The gastric mucosa is known to be capable of repair after mucosal injury by re-epithelialization. This is achieved by sloughing off the damaged cells, rapid migration of viable cells and by cell proliferation to replace the dead cells^[15]. Although aspirin is known to cause GU in the absence of *H pylori*, the very low numbers of *H pylori* negative GU cases in this study might be the reason for not detecting a significant association between aspirin intake and GU.

Although some earlier reports indicated that alcohol intake might reduce the occurrence of peptic ulcers, this was not confirmed by other studies^[5]. It was reported that alcohol consumption, particularly wine consumption may reduce the odds of active infection with *H pylori*^[16].

Brenner *et al*^[17] also indicated that alcohol has a protective effect of consumption against active infection with *H pylori*. Excessive alcohol intake, however, was shown to increase peptic ulcers^[5]. Drinking more than 42 drinks per week increased the risk of a bleeding ulcer fourfold compared with drinking less than one drink per week^[10]. Our results showed that alcohol intake was not an independent factor only when other risk factors involved revealed a significant association with GU and DU irrespective of the presence or absence of *H pylori*. This also indicates that alcohol plays a role in the development of peptic ulcers. The differences in the social habits of smoking and alcohol intake among the Turkish patients might be the reason for the significant prevalence of DU and GU in male patients than in female patients.

In conclusion, the analysis conducted in this study showed that in the presence of *H pylori*, aspirin, alcohol and NSAIDs intake act as independent risk factors that had an augmenting impact on the occurrence of GU. However, only together was such impact observed in the occurrence of DU in Turkish patients.

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