Additive Deleterious Effect of Smoking on Gastroduodenal Pathology and Clinical Course in *Helicobacter pylori*-Positive Dyspeptic Patients

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Abstract

Background: Cigarette smoking has long been regarded as an important factor in the pathogenesis of peptic ulcer disease.

Objective: To investigate whether cigarette smoking has an additive effect on the clinical presentation and course of disease in *Helicobacter pylori*-positive dyspeptic patients.

Patients and Methods: The study group comprised 596 consecutive *H. pylori*-positive dyspeptic patients (334 males and 262 females, mean age 50.6, range 12–81 years). Following upper gastrointestinal endoscopy, patients were subdivided by diagnosis as follows: Non-ulcer patient group (n=312: gastritis 193, duodenitis 119), gastric ulcer (n=19), and duodenal ulcer (n=265). *H. pylori* infection was confirmed by histology and/or rapid urease test. In addition, 244 patients had a positive ^{14}C-urea breath test prior to antimicrobial treatment. The patients' medical history and smoking habits were obtained using a detailed questionnaire completed by the patients and their referring physicians.

Results: There were 337 non-smoking patients, 148 current smokers and 111 past smokers. Gastric and duodenal ulcers were significantly less prevalent in non-smokers than in current or past smokers (gastric 1.8%, 4.1%, 6.3%; duodenal 39.8%, 50%, 51.4%, respectively) ($P<0.05$). The incidence of gastrointestinal bleeding was significantly lower in non-smokers than in current or past smokers (7.1%, 8.1% and 20.7%, respectively) ($P<0.05$). Bacterial density, as assessed by the UBT value in 244 patients, was higher in non-smokers (mean 352.3±273 units) than in past smokers (mean 320.8±199) or current-smokers (mean 229.9±162) ($P<0.05$). Logistic regression analysis revealed that male gender, current smoking, and immigration from developing countries were all significant independent risks for developing duodenal ulcer, while only past smoking was associated with a higher rate of upper gastrointestinal bleeding in the past.

Conclusions: In *H. pylori*-positive dyspeptic patients, current smoking as well as male gender and immigration from developing countries are associated with an increased risk for duodenal ulcer. This effect does not seem to be related to the bacterial density or increased urease activity of *H. pylori* organisms.

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UBT = urea breath test

For many years cigarette smoking has been regarded as an important risk factor for the development of peptic ulcer disease [1]. Early studies showed that cigarette smoking is associated with increased prevalence of duodenal and gastric ulcers, delays ulcer healing and increases the rate of ulcer recurrence following anti-secretory treatment [2–5]. Several mechanisms by which cigarette smoking adversely affects the gastric mucosa have been suggested. These mechanisms include potentiation of gastric aggressive factors, such as acid and pepsin secretion, gastric motility, levels of free radicals and platelet-activating factor, as well as attenuation of defensive factors such as prostaglandin synthesis, gastric mucosal blood flow, mucus secretion and epidermal growth factor [6].

The discovery of *Helicobacter pylori* and its pivotal role in the pathogenesis of peptic ulcer disease had shifted the attention from the other known risk factors [7]. Some studies have disputed the significance of continued smoking in ulcer relapse and have shown that curing *H. pylori* infection has dramatically reduced the relapse rate of peptic ulcer disease regardless of patients' smoking habits [8,9]. Although one study showed an increased rate of *H. pylori* infection among smokers [10], other studies failed to find such a relation [11–13]. This correlates well with the accepted assumption that *H. pylori* infection is acquired in childhood.

In contrast to other risk factors such as consumption of non-steroidal anti-inflammatory drugs, relatively little is known about whether smoking has an additive deleterious effect on *H. pylori* infection. An *in vitro* study has shown that nicotine potentiated *H. pylori* vacuolating toxin activity [14].

The aim of the present study was to investigate the influence of smoking habits on gastroduodenal pathology and ulcer complications in *H. pylori*-positive dyspeptic patients.

Patients and Methods

Subjects

The study included 596 consecutive patients who were referred to our gastroenterology laboratory for evaluation of dyspeptic symptoms and were found to be positive for *H. pylori*. All the patients underwent upper gastrointestinal endoscopy and were diagnosed to have duodenal ulcer, gastric ulcer, or non-ulcer (mainly gastritis or duodenitis), based on the macroscopic findings at endoscopy. *H. pylori* infection was confirmed during endoscopy using rapid urease test (CUTest, Pharma, Temler, Germany) or by histological examination (Giemsa stain). In 244 patients a ^{14}C urea breath test was also performed prior to any antimicrobial treatment.

A detailed questionnaire was completed by the referring physician for all the patients. This included demographic data, past history of peptic ulcer disease including complications such as upper gastrointestinal bleeding, NSAID consumption, and smoking habits. Patients were classified as current smokers if they smoked more than 10 cigarettes per day, and past smokers if they had smoked more than 10 cigarettes per day in the past and had quit smoking more than 6 months previously. Patients using NSAIDs or those who had undergone gastric operation in the past were excluded.

^{14}C-urea breath test

A total of 244 patients underwent ^{14}C-UBT after an overnight fast to confirm *H. pylori* infection. Following a standard test meal to delay gastric emptying (Sustacal, Mead-Johnson, Evansville, IN, USA), the patients ingested 2.5 μCi ^{14}C-urea combined with 250 mg "cold" urea. Breath samples were collected at 30 and 60 minutes. The results were expressed as percentage of administered dose of ^{14}C per mmol of expired $CO_2 x 10^4$. A cumulative test value at 30 and 60 minutes in excess of 50 (% units) was defined as positive for *H. pylori*. The sensitivity and specificity rates with this method in our laboratory were previously reported and reached 87.5% and 100% respectively [15]

Statistical analysis

The rates of ulcer occurrence and upper gastrointestinal bleeding among the various patient groups were compared using the Chi-square test, and a P value of less than 0.05 was considered significant. UBT values are stated as mean ± standard error of mean. The mean test values were compared using Students' t-test. Multiple logistic regression analysis was used to identify variables carrying a significant risk for duodenal ulcer or upper gastrointestinal bleeding. The calculations were performed using Statistix statistical software.

NSAID = non-steroidal anti-inflammatory drug

Results

The study group comprised 596 patients (334 males and 262 females) with a mean age of 50.6±17.2 years (range 12–81). The endoscopic diagnosis was as follows: Non-ulcer (n=312: gastritis 193, duodenitis 119), gastric ulcer (n=19), and duodenal ulcer (n=265). There were 337 non-smoking patients, 148 current smokers and 111 past smokers. The patients' demographic characteristics in the various groups are shown in Table 1. The number of smokers was higher among males than among females, as expected in our community [16]. The average age of current smokers was lower than of non-smokers and past-smokers (42.7 vs. 53.8 and 51.8 respectively). The distribution of the patients according to their place of birth was similar in all patient groups.

Table 2 summarizes the patients' endoscopic diagnosis, history of upper gastrointestinal bleeding and mean urea breath test value in relation to smoking habits. Peptic ulcer was significantly less prevalent among non-smokers than among current or past smokers (gastric 1.8%, 4.1%, 6.3%; duodenal 39.8%, 50%, 51.4%, respectively) ($P<0.05$). The incidence of upper gastrointestinal bleeding was significantly lower in non-smokers than in past smokers (7.1% and 20.7%, respectively) ($P<0.05$). Bacterial density, as assessed by the urea breath test value in 244 patients, was higher in non-smokers (mean 352.3±273 units) than in past smokers (mean 320.8±199) or current smokers (mean 229.9±162) ($P<0.05$ for non-smokers vs. current smokers).

Logistic regression analysis of the various patients' characteristics is shown in Table 3. Current smoking, male gender, and immigration from developing countries were found to be independent risks for duodenal ulcer (odds ratio 1.62, 1.98, 1.5; $P=0.02$, 0.0001, 0.03 respectively), while older age and past smoking were not. However, past smoking was the only significant independent risk factor

Table 1. Demographic data of patients in relation to their smoking habits

	Non-smokers (n=337) No. (%)	Current smokers (n=148) No. (%)	Past smokers (n=111) No. (%)	Total (n=596) No. (%)
Male	157 (46.6)	92 (62.2)	85 (76.6)	334 (56)
Female	180 (53.4)	56 (37.8)	26 (23.4)	262 (44)
M:F	1:0.87	1.64:1	3.26:1	1.27:1
Age (yr)				
Mean	53.8	42.7	51.8	50.6
Range	10–87	18–80	17–87	10–87
Place of birth				
Israel	116 (34.5)	59 (39.9)	38 (34.2)	213 (35.7)
Asia/Africa	46 (13.6)	18 (12.1)	21 (18.9)	85 (14.3)
East Europe	175 (51.9)	71 (48)	52 (46.8)	298 (50)

Table 2. Distribution of gastroduodenal pathology, rate of upper gastrointestinal bleeding and mean urea breath test values in relation to smoking habits

	Non-smokers (n=337) No. (%)	Current smokers (n=148) No. (%)	Past smokers (n=111) No. (%)	Total (n=596) No. (%)
Endoscopic diagnosis				
Non-ulcer	197 (58.4)	68 (45.9)	47 (42.3)	312 (52.4)
Duodenal ulcer	134 (39.8)	74 (50)*	57 (51.4)*	265 (44.5)
Gastric ulcer	6 (1.8)	6 (4.1)	7 (6.3)*	19 (3.2)
History of UGI bleeding	24 (7.1)	12 (8.1)	23 (20.7)*	59 (9.9)
UBT value (dpm units)	352 ± 273	230 ± 162*	321 ± 199	

* $P < 0.05$ in comparison to non-smokers.

Table 3. Logistic regression analysis of factors predicting duodenal ulcer and UGI bleeding

	Duodenal ulcer		History of UGI bleeding	
	Odds ratio (95%CI)	*P*	Odds ratio (95% CI)	*P*
Male gender	1.98 (1.39–2.82)	0.0001	1.44 (0.78–2.66)	NS
Older age	1.01 (1.00–1.02)	NS	1.01 (0.99–1.03)	NS
Current smoking	1.62 (1.07–2.45)	0.02	1.32 (0.62–2.8)	NS
Past smoking	1.45 (0.91–2.3)	NS	3.3 (1.7–6.4)	0.0004
Immigrants from developing countries	1.5 (1.02–2.2)	0.03	1.47 (0.75–2.89)	NS

UGI = upper gastrointestinal, CI = confidence interval, NS = not significant

associated with history of upper gastrointestinal bleeding (OR 3.3, $P=0.0004$).

Discussion

There is general agreement that *H. pylori* infection is the major cause of chronic gastritis and an extremely important contributing factor in the development of peptic ulcer [7]. Several questions concerning the interaction between *H. pylori* infection and cigarette smoking should be addressed: Is cigarette smoking associated with increased prevalence of *H. pylori* infection or with more severe disease in *H. pylori*-infected individuals? Does cigarette smoking influence the eradication rate of *H. pylori* with the various antimicrobial regimens, and does cigarette smoking influence the ulcer relapse rate following successful eradication?

Except for one study that showed a higher rate of *H. pylori* infection in smokers than non-smokers [10], all other studies did not find any correlation between smoking and *H. pylori* colonization [11–13]. The latter correlates well with the current data that *H. pylori* infection is acquired at childhood, at an age when smoking does not play any role. Several studies also showed that smoking does not contribute to ulcer relapse after *H. pylori* eradication [8,9]. Studies on the influence of smoking on *H. pylori* eradication have yielded conflicting results and may depend on the antimicrobial regimens used [17,18]. Surprisingly, there are few data on the relation between smoking and the gastroduodenal pathology in *H. pylori*-positive patients.

While the precise pathogenic mechanisms by which *H. pylori* and smoking cause the mucosal injury are unknown, several possible mechanisms have been suggested. It is therefore reasonable to assume that combinations of both these factors will lead to a more severe injury to the gastroduodenal mucosa.

Martin et al. [11] reported that smoking increases the risk of ulcer formation in *H. pylori*-positive patients, as 73% of their *H. pylori*-seropositive smokers had a duodenal or gastric ulcer compared to only 29% of *H. pylori*-positive non-smokers. McColl et al. [19] reported an increased prevalence of duodenal and gastric ulcers in *H. pylori*-positive dyspeptic smokers (67%) compared to non-smokers (46%).

The findings of the present study confirm those of the studies by McColl and Martin and their teams, and in a much larger patient group. Our study also revealed an increased rate of upper gastrointestinal bleeding in *H. pylori*-positive dyspeptic ex-smokers compared to non-smokers. Upper gastrointestinal bleeding is the most common complication of peptic ulcer disease, with a prevalence of 15 to 20% [20]. Duodenal ulcer complications, such as bleeding and perforation, have been found to be more prevalent among smokers [21]. We found a total rate of 9.9% upper gastrointestinal bleeding in our patients, which was significantly more prevalent in past smokers (20.7%). This variable was the only one that was analyzed retrospectively, and the result may reflect a prolonged cumulative effect of male gender predominance, long duration of smoking in the past, and older individuals comprising this group. A recent survey conducted by the American College of Gastroenterology showed that bleeding patients were significantly older, more likely to be male, and more likely to use alcohol and tobacco [22].

We found that the UBT value was inversely related to smoking and was highest in non-smokers and lowest in current smokers. The UBT value reflects the intragastric urease activity, and according to many authors reflects the extent of *H. pylori* density in the stomach [23,24]. Smoking has been shown to decrease the gastric wall mucus content, thereby exposing the bacteria to the acidic environment inside the stomach and significantly reducing their number.

Animal studies have shown that smoking or intragastric local nicotine application by themselves are not sufficient to produce gastric mucosal damage. However, they can potentiate and aggravate a chemical-induced ulcer [25]. It is reasonable to assume that *H. pylori* infection acquired in

childhood is the initial step causing acute and chronic gastritis, whereas smoking is a contributing factor for later ulcer development and complications.

In conclusion, we found that cigarette smoking increases the risk of peptic ulcer occurrence and upper gastrointestinal bleeding in *H. pylori*-positive male and female patients. These findings identify *H. pylori*-positive smoking dyspeptic patients as a specific high risk patient group that requires *H. pylori* eradication therapy.

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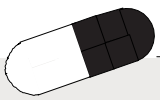
Capsule



Global warming and disease

The alarm has been raised that global warming will inevitably bring an increased threat of vector-borne diseases, such as malaria, to higher latitudes. In contrast, the multivariate approach used by Rogers and Randolph, invoking both temperature and rainfall predictions from the Hadley Centre Global Climate Model, together with knowledge of the ecology of the parasite, suggests that the gains in malaria distribution in 2050 will, in fact, be rather modest, even under extreme conditions of change. Predicted gains are in the southern United States, westward in China, southward in Brazil, and some expansion in central Asia and into Turkey; Europe would remain largely unaffected. Climate has already been thought to play an important role in cholera outbreaks.

Pascual et al. now resolve some of the complexities in cholera dynamics in Bangladesh and show that while climate plays an important role, it is not the entire story. The authors examined an 18 year disease record and found that outbreaks could be related to previous disease level and local temperature.

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