RESEARCH ARTICLE

Clinical Factors Related with *Helicobacter Pylori* Infection - Is there an Association with Gastric Cancer History in First-Degree Family Members?

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Abstract

Background: The aim of this study was to assess clinical factors associated with *Helicobacter pylori* positivity and to evaluate the incidence of gastric carcinoma in first-degree family members of infected patients. A total of 580 patients (mean age:38±17) with gastrointestinal complaints underwent C-14 urea breath test (UBT). Patients were grouped as: Group-1, untreated patients (n:384); and Group-2, patients who previously treated with eradication triple therapy (n:196). C-14 UBT was performed 1-2 months after the completion of eradication therapy. Associations of *H pylori* positivity with age, gender, ABO and Rhesus groups, smoking, dietary habits, and history of gastric cancer in first-degree family members were evaluated. The frequency of *H pylori* positivity was significantly higher in group-1 (58%) compared to group-2 (20%), p=0.001. There were no correlations between *H pylori* positivity and age, gender, ABO groups, Rhesus subgroups, smoking and dietary habits in both patient groups. The frequency of gastric cancer in family members was significantly higher in patients with *H pylori* infection among group-1, compared to infected patients among group-2 (56% vs. 28.6% respectively, p=0.03). We observed a significant association between *H pylori* positivity and the presence of gastric cancer in first-degree relatives of group-1 patients. Our results provide some confirmation of the presence of a link between gastric cancer development and *H pylori*. C-14 UBT is a sensitive, reliable and a widely recommended test for the detection of H pylori infection and recurrence. We suggest that detection and eradication of *H pylori* may contribute to a reduced risk of gastric cancer in the family members of infected patients.

Keywords: *Helicobacter pylori* - gastric cancer - C-14 urea breath test

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Introduction

Helicobacter pylori infection is the most common bacterial infection worldwide (Correa et al., 2008; Kandulski et al., 2008). The prevalence and severity of the infection vary among populations. The prevalence of *H pylori* infection is about 80% in developing countries and 20-50% in developed countries. Epidemiologic studies on *H pylori* infection in Turkey demonstrated that its prevalence is 67-81% which is similar to that of developing countries (Us et al., 1998; Aydin et al., 2000). The prevalence of *H pylori* may vary considerably with age, socioeconomic status, gender, ABO blood groups and smoking (Graham et al., 1991; Sitas et al., 1991). However, in the literature, there are conflicting results on the association between *H pylori* infection, ABO blood groups, age and gender (Loffeld et al., 1991; Niv et al., 1996).

The presence of *H pylori* infection is closely related to chronic gastritis which significantly increases the risk of developing peptic ulcer, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Veldhuyzen et al., 1994; Correa et al., 2007; Kandulski et al., 2008). It is estimated that individuals infected with *H pylori* have more than two-fold increased risk of developing gastric cancer compared with non-infected ones (Queiroz et al., 2012). Moreover, several studies have shown an increased risk of developing gastric cancer in relatives of patients with the infection (Brenner et al., 2000; Queiroz et al., 2012). As *H pylori* infection plays an important role in gastric cancer pathogenesis, the elimination of *H pylori* has great importance. Evidences point out a significant reduction in the risk of gastric cancer development following *H pylori* eradication (Mera et al., 2005; Take et al., 2005; Fuccio et al., 2009). More accentuated in wealthy societies, a steady decrease in the prevalence of *H pylori* infection and the incidence of gastric cancer has been observed in most populations in recent decades (Correa et al., 2008).

The C-14 urea breath test (UBT) is a non-invasive, sensitive, safe and highly reliable test for the detection of *H pylori* infection. UBT has been widely used to diagnose *H*

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pylori infection, to confirm eradication after treatment and to detect re-infection (Desroches et al., 1997; Ahuja et al., 1998). The accuracy of UBT in the detection of *H pylori* infection is known to be higher than that of stool antigen tests and immunological tests (Gisbert et al., 2004). On the basis of these evidences, Management of *Helicobacter pylori* infection-The Maastricht IV/Florence Consensus Report recommends the routine use of C-14 UBT for *H pylori* infection, and test-and-treat strategy where the *H pylori* prevalence is high (≥20%) (Malfertheiner et al., 2012).

In this study, grouping the patient population as the patients who were not previously treated with *H pylori* eradication therapy and the ones who recently received eradication triple therapy, we aimed to evaluate the clinical factors associated with *H pylori* positivity. In addition, we aimed to evaluate the incidence of gastric carcinoma in first-degree family members of patients infected with *H pylori* among both groups.

Materials and Methods

A total of 580 patients (426 F, 154 M, mean age: 38±17, range: 8-67) with gastrointestinal complaints who were referred to our department for C-14 UBT between November 2011 to June 2012 were enrolled in this study. Patients who had so-called alarm symptoms (weight loss, dysphagia, overt gastrointestinal bleeding, abdominal mass and iron deficient anemia), patients who had previous gastric surgery and patients with a history of gastric carcinoma were not included in this study.

Patients were grouped as; Group 1: patients who did not have previous *H pylori* eradication therapy (n: 384) and, Group 2: patients who previously treated with *H pylori* eradication triple therapy (amoxicillin-clarithromycin- proton pump inhibitor) for 14 days (n: 196). C-14 UBTs were performed 1-2 months after the completion of eradication therapy in group 2 patients.

Antacids and H2 receptor antagonists were stopped at least 24 hours before C-14 UBT. Proton pump inhibitors and sucralfate were discontinued 2 weeks, antibiotics were discontinued 4 weeks prior to test. After overnight fasting, patients were asked to swallow 37 kBq (1 μCi) of encapsulated C-14/citric acid composition (Helicap, Noster system, Stockholm, Sweden) with 50 ml water. Breath samples of patients were collected with a special dry cartridge system (Heliprobe Breathcards, Noster system) for 10 minutes after administration of C-l4 urea. Patients exhaled into the breath card until the indicator color changed from orange to yellow. The breath card was inserted into Heliprobe analyses and the activity was counted for 250 seconds. Results were expressed both as counts per minutes (cpm) and grade. Counts <25 cpm were defined as 0: not infected, counts between 25 and 50 cpm as H1: equivocal, and counts >50 cpm as H2: infected.

The associations of *H pylori* positivity and clinical factors such as age, gender, ABO blood groups and Rhesus subgroups, smoking and dietary habits, as well as history of gastric cancer in family members were evaluated.

All patients were asked to sign informed consent forms after the test information has been fully explained and the study was approved by the ethics committee of our institution.

Statistical analysis

The relationship between *H pylori* positivity and clinical factors such as gender, blood groups, smoking and dietary habits, history of gastric cancer in family members were analyzed by chi-square test. Comparison of *H pylori* infection frequencies in between groups were analyzed by chi-square test. The relationship between *H pylori* positivity and age was analyzed with Man Whitney U test. A p-value of <0.05 was considered statistically significant.

Results

Demographic data of all patients is given in Table 1. The frequency of *H pylori* positivity was 53.6% in the patient population. The frequency of *H pylori* positivity was 58% (223/384) in untreated patients (group 1), and 20% (40/196) in patient group who received eradication therapy (group 2). We observed that *H pylori* positivity was significantly higher in group 1 compared to group 2, p=0.001.

The frequency of *H pylori* positivity was 48.1% in males and 45.8% in female patients in the study population. We observed no correlations between *H pylori* positivity and gender (p>0.05). Likewise, there were no correlations between patient age and *H pylori* positivity (p>0.05) (Table 2).

We found that the positivity for *H pylori* infection in group 1 was 60%, 55%, 50% and 48.3% for patients with blood groups A, B, AB and O, respectively, p>0.05. Similarly, the frequency of *H pylori* positivity in group 2 patients was 17%, 9%, 30% and 23.9% in blood groups A, B, AB and O, respectively with p>0.05. The frequency of *H pylori* infection was 55% vs. 44.4% for Rh(+) and Rh(-) patients among group 1 respectively, whereas 18.5% vs. 22.2% among group 2 patients respectively. We observed that the presence of *H pylori* infection did not correlate with ABO blood groups and Rh subgroups when analyzed in the general patient population and separately in groups,

Table 1. Patient Characteristics

		All patients (n: 580) n %	Group 1 (n: 384) n %	Group 2 (n:196) n %
Age		38±17.0	36±17.0	42±15.0
Gender	Male	154 (27.0)	108 (28.0)	46 (270.0)
	Female	426 (73.0)	276 (72.0)	150 (73.0)
Blood groups	A	224 (38.6)	150 (38.6)	74 (37.6)
	B	96 (16.5)	61 (16.1)	35 (17.6)
	AB	49 (8.4)	34 (8.8)	15 (8.0)
	O	211 (36.5)	139 (36.5)	72 (36.8)
Rhesus subgroups	Rh+	411 (88.0)	342 (89.0)	169 (86.0)
	Rh -	69 (12.0)	42 (11.0)	27 (14.0)
Smoking history	Smoker	131 (22.5)	92 (24.0)	39 (20.0)
	Non-smoker	449 (77.5)	192 (76.0)	157 (80.0)
Dietary habits	Home made food consumers	327 (56.0)	223 (58.0)	104 (53.0)
	Fast food consumers	253 (44.0)	161 (42.0)	92 (47.0)
Presence of gastric cancer history in family members		62 (10.6.0)	34 (9.0)	28 (14.0)

Table 2. The Frequency of H pylori Infection with Regard to Clinical Characteristics among Patient Groups

	All Patients (n: 580) %	Group 1 (n: 384) %	Group 2 (n:196) %	p
Age (mean±std)	38±17	36±17	38±15	>0.05
Gender				>0.05
Male	48.10	58.30	19.50	
Female	45.80	57.90	20.60	
Blood groups				>0.05
A	46.90	60	17	
B	41.90	55	9	
AB	43.80	50	30	
0	41.60	48.30	23.90	
Rhesus subgroups				>0.05
Rh +	37.80	55	18.50	
Rh -	44.50	44.40	22.20	
Smoking history				>0.05
Smoker	54.20	55.80	25.60	
Non-smoker	44.10	65.20	19	
Dietary habits				>0.05
Home made food consumers				
	48	40	24.20	
Fast food consumers	40	39	24.10	
Presence of gastric cancer in first-degree family members				
	43.50	56	28.60	0.03

p>0.05 (Table 2).

Similarly, we observed no correlation between *H pylori* infection and smoking habits both in groups and in the whole study population. In group 1, the frequency of *H pylori* positivity was 55.8% in smokers and 65.2% in nonsmokers group, p>0.05. Likewise, *H pylori* positivity was 25.6% in smokers and 19% in nonsmokers in group 2, p>0.05.

The patients' dietary habits were questioned as follows; those consuming mostly home made food (fast food consumption less than once a week) and those consuming fast food at least four times a week. *H pylori* positivity was 48% in patients consuming mostly home made food and 40% in patients who consume fast food in the study population. We observed that there was no significant difference between *H pylori* positivity in patients with regard to dietary habits both in the general population and in patient groups (Table 2).

In the study population, 62 patients (10%) had a positive history of gastric cancer in first-degree family members. The rate of family-members who had previously undergone *H pylori* eradication therapy was 20.4 % in group 18.9% in group 2 (p>0.05). Among patients who were not treated with *H pylori* eradication (group 1), 34 patients (8%) had a positive history of gastric cancer in first-degree family members. Of these, 19 patients (56 %) were infected with *H pylori*. Among patients who previously treated for *H pylori* infection (group 2), 28 patients (14%) had a positive history of gastric cancer in first-degree family members. Of these, 8 patients (28%) had a positive history of gastric cancer in first-degree family members. Among patients infected with *H pylori* , the frequency of gastric cancer history was significantly higher in family members of patients who did not treated

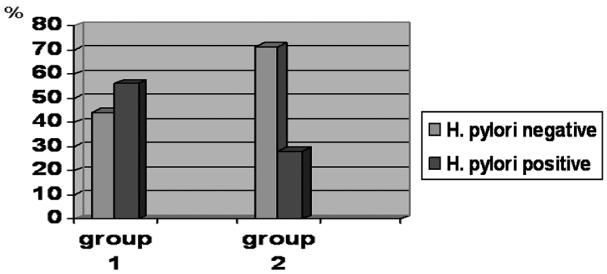

Figure 1. C–14 urea Breath test Results in Group 1 and Group 2 Patients Who had Positive Gastric Cancer History in First-Degree Family Members

with *H pylori* eradication therapy compared to previously treated patients (p=0.03, Table 2). In addition, we observed a significant association between *H pylori* infection and the presence of gastric cancer history in first-degree relatives of untreated patients (p=0.03) (Figure 1).

Discussion

H pylori infection is the most common chronic bacterial infection worldwide. Today it is widely accepted that *H pylori* is not only a cause of chronic gastritis, duodenitis and peptic ulcer disease, but also plays role in the etiopathogenesis of gastric carcinoma (Veldhuyzen et al., 1994; Correa et al., 2007; 2008; Kandulski et al., 2008). Moreover, *H pylori* infection has been reported to be responsible from several extra gastric pathologies such as hematological, cardiovascular, cerebrovascular, lung, hepatobiliary, intestinal, neurological diseases (Bohr et al., 2007).

Arising from the wide spectrum of *H pylori* -related diseases, patient based risk factors for *H pylori* infection have been an important subject of research. Factors such as patient age, gender, ABO blood types, socioeconomic status, household crowding, home sanitation, changes in dietary habits and control of non *H pylori* infection diseases are among the most evaluated factors for the association with *H pylori* infection. However, there is lack of consensus on the association between *H pylori* prevalence and some of these factors such as age and gender. Even though recent epidemiological studies report an age-dependent increase in *H pylori* positivity, various studies describe that the prevalence of *H pylori* infection does not differ with age (Graham et al., 1991; The EUROGAST Study Group., 1993; Moayyedi et al., 2002; Rodrigues et al., 2005). Similar controversies exist on the association between *H pylori* positivity and gender. Although some studies have found higher prevalence of *H pylori* infection in males, various studies report the opposite (The EUROGAST Study Group., 1993; Mégraud et al., 1993; Broutet et al., 2001; Wu et al., 2003; de Martel et al., 2006). In this study, we found that age and gender were not related with *H pylori* positivity both for untreated patients and for patients who previously received eradication therapy.

Likewise, in this study we did not observe any association between *H pylori* positivity and ABO blood groups as well as Rh factors. There are conflicting results on the association of *H pylori* infection and ABO

groups in the literature. Blood group O was reported to be associated with duodenal ulcer disease, while gastric ulcer and gastric carcinoma were associated with blood group A (Smith et al., 1994). In addition, the Lewis-blood group antigen has been shown to function as a receptor for *H pylori* adhesions, mediating bacterial adherence to the gastric epithelial surface, which is essential for bacterial colonization (Boren et al., 1993). On the contrary, several studies report that they found no association between *H pylori* infection and blood groups (Sharara et al., 2006; Seyda et al., 2007).

In the present study, we observed that there was no association between *H pylori* infection and smoking habits of patients. Beyond the influence on *H pylori* infection, recent literature emphasize on the contribution of smoking behavior to the increased risk of gastric carcinogenesis from gastric atrophy (Hishida et al., 2010). However, evidence from recent literature suggests that smoking is one of the factors associated with therapy failure in *H pylori* eradication (Suzuki et al., 2006; Gasparetto et al., 2012). The most possible cause may be attributable to a reduction in antibiotic delivery due to decreased gastric blood flow and decreased in intragastric pH in cases of smoking (Malfertheiner et al., 2012).

We observed that consuming mostly home made food or fast food was not significantly associated with *H pylori* positivity in our patient group. Regardless of the presence of *H pylori* infection and its virulence, studies have proved that improved dietary habits such as reduced salt intake, more consumption of fruits and fresh vegetables, improvements in refrigeration at home and increased use of vitamin and probiotic bacteria rich products have lowered the risk for gastric cancer development. In this study, we did not find an obvious link between *H pylori* infection and dietary habits and smoking behavior of our patients (Correa et al., 2008; Peleteiro et al., 2011). Besides, evidence from growing number of studies point out the role of smoking and dietary habits in gastric carcinogenesis rather than their association with *H pylori* infection.

In this study, the frequency of *H pylori* infection was 20% in patients who received eradication therapy for *H pylori*. Positive results for *H pylori* infection is thought to occur via two distinct mechanisms, recurrence and re-infection. Management of *Helicobacter pylori* infection-The Maastricht IV/Florence Consensus Report agree on the fact that the relapse rate seen in 6 months or the year after *H pylori* eradication is mainly related to recurrence of the same infection rather than a true re-infection (Malfertheiner et al., 2012). There is overwhelming evidence that C-14 UBT is an excellent test for follow-up after *H pylori* eradication (Malfertheiner et al., 2012). Even though the factors related to therapy failure was not the subject of this study, we considered that the relatively high incidence of positive UBT results in treated patients may be originated from inadequate use of drug doses or even drugs themselves or failure to provide hygienic conditions. In addition, given the higher incidence of *H pylori* infection in developing countries as our population, we considered that these results were in parallel to the recent literature (Us et al., 1998; Aydin et al., 2000).

One important result of this study was the association of *H pylori* positivity and the presence of gastric cancer history in family members of patients who did not previously treated for *H pylori* eradication. Today, it is widely known that the primary route for *H pylori* infection is the fecal-oral and person-to person transmission pattern. This pattern along with the present results indicate that bad environmental hygienic conditions and close intra-familial relationships are important in *H pylori* contamination (Sari et al., 2008) which triggers the so-called Correa cascade to gastric mucosal atrophy, intestinal metaplasia, and finally to development of gastric carcinoma. It is known that *H pylori* infection with cytotoxin-associated (CagA) gene positive strains has been related with increased risk for development peptic ulcer and gastric carcinoma (Blaser et al., 1995; Parsonnet et al., 1997). Recent studies demonstrated the association with cagA positive *H pylori* and the higher rate for development gastroduodenal disease, in Turkish population (Sezikli et al., 2006; Salih et al., 2007).

Thus, combining the fact that increased prevalence of *H pylori* infection among family members and the observed association of *H pylori* infection with the presence of gastric cancer in family members in this study may support the researches which suggest that host genetics may count for the development of gastric cancer (El-Omar et al., 2001; Vieth et al., 2006). Authors report that the host immune response has a strong role in determining the outcome of *H pylori* infection, and the polymorphisms in genes that control this immune response have been shown to affect the risk for gastric cancer (El-Omar et al., 2001; 2003; Vieth et al., 2006;).

The genetic variations between the gastritis and gastric carcinoma patients may play important roles in the *H pylori* -related clinical outcomes. There are several studies which demonstrated that the polymorphisms of the NOD1 (nucleotide-binding oligomerization domain) and NOD2 genes in different populations were related to variant clinical outcomes of *H pylori* infection. Moreover, it was shown that NOD1 and NOD2 genes polymorphisms and/or mutation induced the incidence of gastric carcinoma in different populations, in recently reports (Wang et al., 2012; Zhang et al., 2012). The risk for the development of gastric cancer in patients with a family history of gastric cancer has been reported to be as high as 1.6-2.6 folds (Kondo et al., 2003; Kawasaki et al., 2007). The recent literature have proved that relatives of gastric cancer patients are more frequently colonized by the most virulent *H pylori* cagA and vaculating cytotoxin (vacA) genotypes, which may increase their risk of gastric cancer when act together with genetic factors (Queiroz et al., 2012). In this content, the observed higher incidence of gastric cancer in family members in this study may provide some confirmation of the presence of a genetic link between the *H pylori* infection and gastric cancer. However, this study may have been limited by the lack of *H pylori* strain analysis and genetic evaluations of the patient population along with the family members due to its retrospective nature.

On the contrary, in this study, among patients infected with *H pylori* , the frequency of gastric cancer history

was significantly lower in family members of patients who previously treated with *H pylori* eradication therapy compared to untreated patients even though the proportion of family members who previously received eradication therapy were comparable between two groups. Today, it is widely accepted that successful eradication of *H pylori* infection reduces the risk for gastric cancer development (Malfertheiner et al., 2012). In addition, according to the Management of *Helicobacter pylori* infection-The Maastricht IV/Florence Consensus Report, *H pylori* eradication to prevent gastric cancer should be considered in the first-degree relatives of family members with a diagnosis of gastric cancer (Malfertheiner et al., 2012). We considered that our findings; the lack of association between *H pylori* infection and gastric cancer history in family members of patients who had previous *H pylori* eradication therapy in contrast to the association of *H pylori* infection and gastric cancer history in family members in untreated patients suggest that eradication therapy may have broken the *H pylori* – related cascade for gastric cancer development. In addition, we considered that the findings of our study are in parallel to the recent literature and may highlight the importance of *H pylori* eradication therapy for high risk patients.

In conclusion, the detection, eradication and post-therapy control of *H pylori* infection is important for reducing the risk for development of gastric precancerous lesions and cancer especially in populations in which higher prevalence of *H pylori* infection and gastric carcinoma is observed. The C-14 UBT is a sensitive, reliable and a widely recommended test for the detection of *H pylori* infection and to confirm eradication after treatment as well. We considered that, the results of this study provide some confirmation of the presence of a link between gastric cancer development and *H pylori* caused by genetic, epigenetic and environmental factors. In addition, our results also suggest that detection and successful eradication of *H pylori* may contribute to the reduction of gastric cancer risk in the family members of infected patients.

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