

H pylori

***H pylori* infection and reflux oesophagitis: A case-control study**

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CONCLUSION: *H pylori* infection cannot prevent GORD in this region.

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Abstract

AIM: To examine the relationship between *H pylori* and gastro-oesophageal reflux disease (GORD) in Iran.

METHODS: In this study 51 GORD patients (referred to endoscopy at Taleghani hospital) were compared with 49 age-sex matched controls. Diagnosis of *H pylori* was made by gastric mucosal biopsy and rapid urease test (positive if the result of one or both diagnostic methods was positive). Updated Sydney system was used to report histopathological changes.

RESULTS: The frequency of *H pylori* infection based on rapid urease test and histology was 88.2% (45) in patients and 77.6% (38) in controls, which showed no significant difference. The frequency of *H pylori* infection was significantly higher in the antrum than in the corpus and cardia. The mean activity, inflammation, and gastritis scores were also higher in the antrum of patients than in the antrum of controls. The mean scores were significantly higher in the corpus of controls than in the corpus of patients. Diffuse active gastritis was observed in a significantly larger number of controls, while the frequency of diffuse chronic gastritis was higher in patients. There was no significant difference in the frequency of other histological findings between patients and controls.

INTRODUCTION

Heartburn is a common symptom in the general population^[1,2] and is associated with the development of adenocarcinoma of the oesophagus and cardia^[3]. Gastritis-associated hypochlorhydria may protect against gastro-oesophageal reflux disease (GORD)^[4,5]. It has hypothesized that the declined *H pylori* infection results in a decline in peptic ulcer and a concomitant increase in reflux disease and associated oesophageal adenocarcinoma^[6,7]. However, the relationship between *H pylori* infection and GORD has not been established^[8-11]. It was reported that prospective, large studies are needed to explore the *H pylori*-gastro-oesophageal disease relationship further and to avoid confusing potential benefits with known risks^[9-12].

The main of this study was to investigate whether there is a difference between the frequencies of *H pylori* infection in cases and controls, and the possible relationship between *H pylori* infection and GORD.

MATERIALS AND METHODS

Patients

In this study, patients with a history of heartburn, at least two times a week for a period of more than 3 mo, referred for gastrointestinal endoscopy at Taleghani Hospital, Shaheed Beheshti University of Medical Sciences, between March 2001 and February 2002, were enrolled. The reflux oesophagitis group included 51 patients (31 men and 20 women, mean age, 54.1 ± 17.2 years, range 17-80 years) with endoscopically diagnosed erosive reflux oesophagitis.

Table 1 Frequency of *H pylori* infection in two groups *n* (%)

Group	<i>H pylori</i>			Rut	Diagnosis of <i>H pylori</i>	Total
	Cardia	Corpus	Antrum			
Case	27 (52.9)	25 (49.0)	37 (72.5)	23 (45.1)	45 (88.2)	51 (100.0)
L.A. classification						
A	11 (21.6)	8 (15.7)	12 (23.5)	9 (17.7)	16 (31.4)	17 (33.3)
B	11 (21.6)	11 (21.6)	17 (33.4)	12 (23.5)	21 (41.2)	24 (47.1)
C	4 (7.8)	5 (9.8)	7 (13.7)	2 (3.9)	7 (13.7)	9 (17.7)
D	1 (1.9)	1 (1.9)	1 (1.9)	0	1 (1.9)	1 (1.9)
Control	28 (57.1)	27 (55.1)	31 (63.3)	22 (44.9)	38 (77.6)	49 (100.0)
Total	55 (55.0)	52 (52.0)	68 (68.0)	45 (45.0)	83 (83.0)	100 (100.0)

Patients with a history of upper gastrointestinal (GI) surgery, malignancy, oesophageal varices, and antibiotics or bismuth consumption during the last 6 mo, together with those using H₂ blockers, proton pump inhibitors (PPIs), alcohol, or non steroidal anti inflammatory drugs (NSAIDs) during the last 4 wk, were excluded from the study. The control group comprised: 49 asymptomatic patients (29 men and 20 women, mean age, 52.2 ± 17.1 years, range 18-80 years) without reflux oesophagitis, any symptom of upper GI diseases, and any lesion in their endoscopy, which was performed for other reasons (work up for iron deficiency, possible malignancy, and ERCP, sphincterotomy, or stone extraction candidates). Two cases of control group were missed during the study. The cases and controls were sex and age matched with a maximum difference of less than 3 years. Written informed consent was obtained for all upper endoscopy and biopsy procedures. This study was approved by the Ethics Committee of the Research Center of Gastroenterology and Liver Diseases, Shaheed Beheshti University of Medical Sciences.

Endoscopy and gastric biopsies

Endoscopy was performed for both case and control groups, by two endoscopists blinded to the status of the controls and patients. The presence and grading of reflux oesophagitis were determined according to L.A. classification, from A (least severe) to D (most severe)^[13]. During endoscopy, two biopsies were taken from the antrum, corpus, and cardia, and stained with standard haematoxylin/eosin and Geimsa to identify *H pylori* and histopathological changes. Rapid urease test was performed on the biopsy specimens from antrum, corpus, and cardia. The urease test was considered positive when the urea solution changed from yellow to pink at room temperature within 24 h. The diagnosis of *H pylori* infection was made by positive findings on either histology or urease test. Patients were considered to be *H pylori*-positive if the result of one or both diagnostic methods was positive and *H pylori*-negative if both methods revealed negative results.

For histopathological analysis, biopsy specimens were fixed in 40 g/L neutral-buffered formaldehyde and embedded in paraffin. Five-micron thick sections were cut from each paraffin block and stained with haematoxylin and eosin for routine histology. Two pathologists blinded to the clinical information of subjects assessed the histopathological changes independently. Updated Sydney

system was used to report histopathological changes^[14]. The degrees of inflammation and activity were scored from 0 (absent) to 3 (most severe). The inflammation score and activity score were summed and expressed as the gastritis score. The predominance for the anatomic regions in gastritis was determined based on the degree of inflammation in the different anatomic parts of the stomach. If the degree of inflammation was higher, the anatomic place with a higher grade of inflammation was stated as the predominant region. For the diagnosis of multifocal atrophic gastritis, we determined intestinal metaplasia or significant mucosal atrophy. Because of the low reproducibility for routine grading of mucosal atrophy, atrophy score was not used as a marker for grading^[14].

Statistical analysis

Results were expressed as mean ± SD. Odd's ratios (95% CI) were calculated to evaluate the differences in the frequency of *H pylori* infection and other histological findings between patient and control groups. Cochran's Q test was used to compare the frequency of *H pylori* infection in the cardia, corpus, and antrum. Mann-Whitney *U* test was used to analyze the differences in activity, inflammation, and gastritis scores between the two groups and Friedman test was used to analyze the different scores in the cardia, corpus, and antrum. *P* < 0.05 was considered statistically significant.

A sample size of about 50 for patient and control groups was considered to have an 80% detecting rate (at the two-sided 5% level) with at least a 25% difference in the prevalence of *H pylori* between the two groups.

RESULTS

Among the 51 reflux oesophagitis patients, 17 (33.3%) were in grade A, 24 (47.1%) in grade B, 9 (17.6%) in grade C, and 1 (1.9%) in grade D (Table 1). Hiatal hernia was observed in 30 (58.8%) patients. The prevalence of *H pylori* infection is shown in Table 1. The frequency of *H pylori* in the antrum was significantly higher than that in the corpus and cardia of the patients (*P* < 0.01), while the differences were not significant in different regions of stomach of the controls, which might be due to the inadequate sample size. We were not able to find any significant difference in the frequency of *H pylori* infection between the two groups (OR: 2.2, 95% CI: 0.7-7.4) as shown in Table 2.

The different histological findings in patients and

Table 2 Different histological findings in two groups *n* (%)

Histological finding	Case	Control	Total	OR (95% CI)
<i>H pylori</i> infection ¹	45 (88.2)	38 (77.6)	83 (83.0)	2.2 (0.7-7.4)
Chronic inflammation in cardia	14 (27.5)	18 (36.7)	32 (32.0)	0.7 (0.3-1.7)
Chronic inflammation in corpus	8 (15.7)	22 (44.9)	30 (30.0)	0.2 (0.1-0.6)
Chronic inflammation in antrum	28 (54.9)	30 (61.2)	58 (58.0)	0.8 (0.3-1.8)
Overall gastritis categorization (Sydney classification)				
Diffuse chronic active gastritis	15 (29.4)	26 (53.1)	41 (42.0)	0.4 (0.2-0.9)
Cardia predominant chronic active gastritis	1 (2.0)	1 (2.0)	2 (2.0)	0.9 (0.0-36.3)
Corpus predominant chronic active gastritis	0	1 (2.0)	1 (1.0)	0.0 (0.0-16.9)
Antrum predominant chronic active gastritis	3 (5.9)	5 (10.2)	8 (8.0)	0.6 (0.1-2.9)
Multifocal metaplastic or atrophic gastritis	1 (2.0)	1 (2.0)	2 (2.0)	0.9 (0.0-36.3)
Chronic carditis	1 (2.0)	2 (4.1)	3 (3.0)	0.5 (0.0-6.9)
Diffuse chronic gastritis	10 (19.6)	2 (4.1)	12 (12.0)	5.7 (1.1-40.4)
Normal	20 (39.2)	11 (22.4)	31 (31.0)	2.2 (0.9-5.8)
Total	51 (100.0)	49 (100.0)	100 (100.0)	-

¹Based on histology and rapid urease test.

controls are shown in Table 2. The frequency of chronic inflammation in the corpus was significantly higher in controls than in patients (OR: 0.2, 95% CI: 0.1-0.6). Diffuse active gastritis was also observed in controls (OR: 0.4, 95% CI: 0.2-0.9), while diffuse chronic gastritis was observed in patients (OR: 5.7, 95% CI: 1.1-40.4). The frequency of intestinal metaplasia and mucosal atrophy was not significantly different between the two groups (Table 2).

The inflammation, activity, and gastritis scores in both groups are depicted in Table 3 and Figure 1. The mean activity score in the cardia, corpus, and antrum of controls was significantly higher than that of patients ($P < 0.01$ or $P < 0.001$, Figure 1A). The inflammation score was higher in the corpus of controls than that in patients ($P < 0.01$, Figure 1B), while the inflammation score of the cardia and antrum was not significantly different between the two groups. Similarly gastritis score was significantly higher in controls than in patients ($P < 0.01$ and $P < 0.05$, Figure 1C).

The mean activity score was significantly higher in the antrum than in the corpus and cardia of controls ($P < 0.001$, Table 3), while the differences were not significant in patients probably due to the inadequate sample size. The mean inflammation and gastritis scores were also significantly higher in antrum than in corpus and cardia of both patients and controls ($P < 0.001$, Table 3). These findings together with the higher frequency of *H pylori* infection in the antrum indicated that *H pylori* in antrum could induce inflammation.

DISCUSSION

Increasing attention has been paid to the relationship between *H pylori* infection and reflux oesophagitis in recent years. GORD is a common condition affecting 25%-40% of the population^[2]. The presence of hiatal hernia^[15], transient relaxation of the lower oesophageal sphincter^[16,17], and impaired clearance of regurgitated gastric contents in the oesophagus^[18] are considered possible causative factors for GORD.

There is evidence that infection with *H pylori* is the principal cause of peptic ulcer disease^[10]. However, there

Table 3 Scores of inflammation, activity, and gastritis in two groups

Group	Cardia	Corpus	Antrum	<i>P</i>
	Median (range)			
Case				
<i>H pylori</i> <i>n</i> (%)	27 (52.9)	25 (49.0)	37 (72.5)	0.005 ¹
Activity score	0 (0-2)	0 (0-2)	0 (0-3)	0.057 ²
Inflammation score	1 (0-2)	1 (0-2)	2 (0-3)	0.000 ²
Gastritis score	0 (0-4)	1 (0-4)	2 (0-6)	0.000 ²
Control				
<i>H pylori</i> <i>n</i> (%)	28 (57.1)	27 (55.1)	31 (63.3)	0.465 ¹
Activity score	1 (0-2)	1 (0-3)	1 (0-3)	0.000 ²
Inflammation score	1 (0-3)	1 (0-3)	2 (0-3)	0.000 ²
Gastritis score	2 (0-5)	2 (0-6)	3 (0-6)	0.000 ²

¹Cochran's Q test; ²Friedman test.

is uncertainty about the role of this organism in GORD and the available data do not demonstrate an evident association between these two factors, although an etiologic link has been found between *H pylori* infection and GORD or peptic oesophagitis^[10]. The prevalence of *H pylori* infection in patients with GORD in our study (88.2%) was higher than that reported in other studies^[9], suggesting that *H pylori* infection is more frequent in developing countries than in industrialized countries^[19].

No difference was found in the prevalence of *H pylori* between patients with reflux oesophagitis and controls in this study. Conflicting evidence about the association of *H pylori* infection with GORD has been reported and geographical location is an important determinant^[9]. The pathogenic role of *H pylori* in reflux oesophagitis is suspected in earlier studies^[20] while other studies have found no relationship between *H pylori* prevalence in GORD patients with that reported in other patients^[10,21-34]. In contrast, the possible protective role of *H pylori* in reflux oesophagitis and other GORD-related diseases such as Barrett's oesophagus and oesophageal adenocarcinoma has recently been suggested^[35-39]. *H pylori* can cause chronic gastritis in virtually all infected people. This persistent inflammation ultimately leads to loss of the normal architecture of gastric mucosa, disappearance of gastric

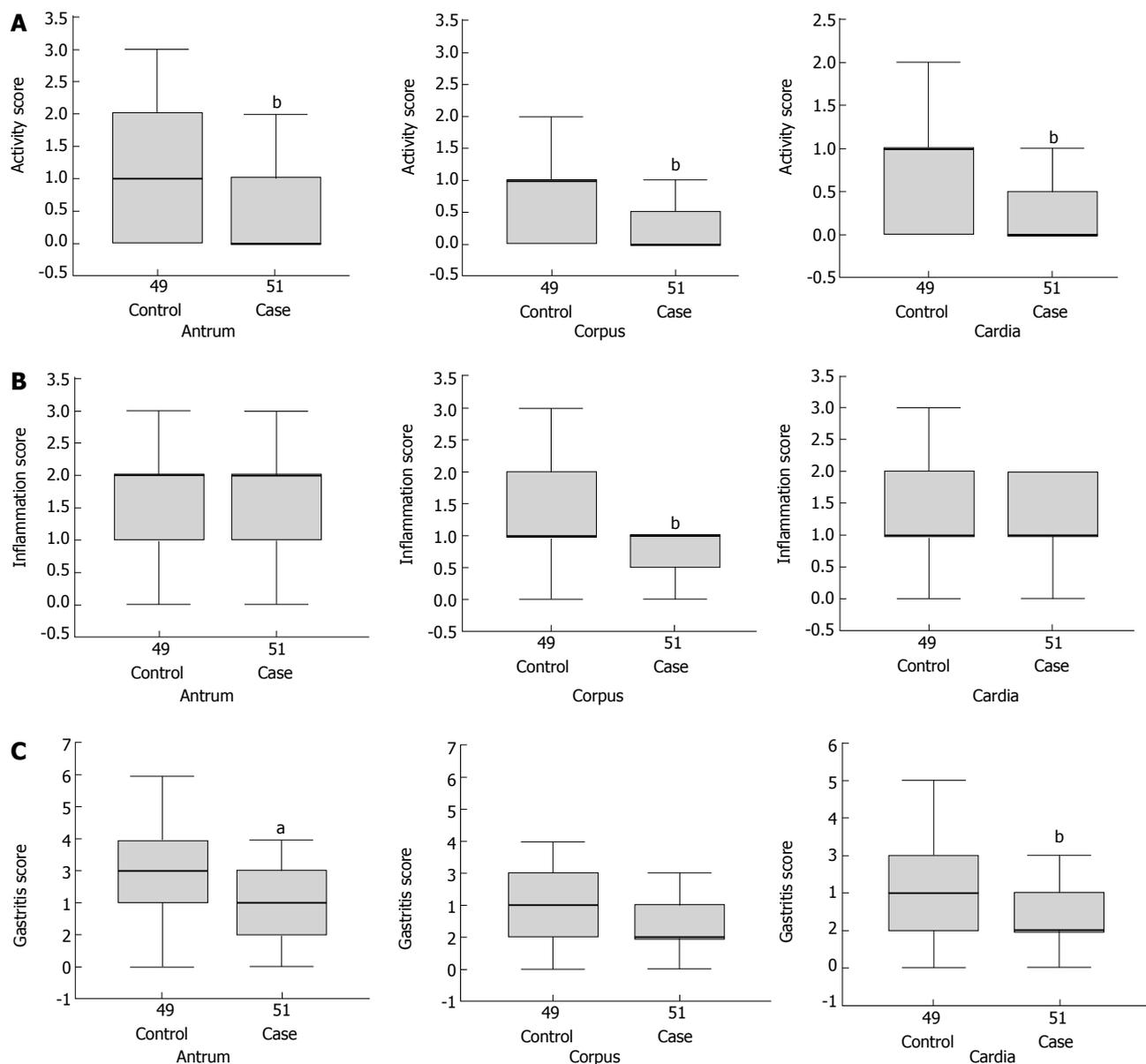


Figure 1 Scores of activity (A), inflammation (B), and gastritis (C) in the antrum and corpus of patients and controls. ^a $P < 0.05$, ^b $P < 0.01$ vs controls.

glands and specialized cells^[40]. Diffuse active gastritis was observed in controls while diffuse chronic gastritis was observed in patients in the present study, suggesting that active inflammation might play a protective role in GORD. Chronic antrum-predominant gastritis has been shown to be associated with secretion of acid and formation of duodenal ulcer^[8,41]. In patients otherwise predisposed to reflux disease, antrum-predominant gastritis may therefore increase acid production and reflux disease development^[8]. On the other hand, atrophy induced by chronic *H pylori* infection (chronic corpus gastritis) with decreased gastric acid production can protect against reflux oesophagitis^[8,11,42]. As a consequence, the antrum predominant inflammation might be considered a factor for *H pylori* infection.

In conclusion, *H pylori* infection is not associated with DORD. Multicentre prospective studies with a larger sample size are needed to explore the relationship between *H pylori* infection and DORD.

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