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Association of *Helicobacter pylori* infection with gastroesophageal reflux disease

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Abstract

Objective: Many studies have shown that *Helicobacter pylori* (*Hp*) is negatively correlated with gastroesophageal reflux disease (GERD). Moreover, some studies deny that eradication of *Hp* increases the incidence of GERD. Therefore, we investigated the association of *Hp* infection with GERD.

Methods: In this retrospective analysis, patients with peptic ulcers were used as a blank control group. We used logistic regression to analyze the relationship between *Hp* infection and GERD. We analyzed 953 patients with peptic ulcers, 180 patients with both peptic ulcers and GERD, and 298 patients with GERD.

Results: Among the patients with GERD, 75.6% (136/180) and 36.2% (108/298) of those with and without peptic ulcers, respectively, had *Hp* infection, and the difference was statistically significant. Among patients with peptic ulcers, 75.6% (136/180) and 67.4% (642/953) of those with and without GERD, respectively, had *Hp* infection. The incidence of GERD in patients with *Hp*-positive and -negative peptic ulcers was 17.5% (136/778) and 12.4% (44/355), respectively. These differences were also statistically significant.

Conclusion: In the analysis of patients with GERD, the prevalence of *Hp* infection was higher among patients with than without peptic ulcers.

Keywords

Helicobacter pylori, gastroesophageal reflux disease, peptic ulcers, infection, association, retrospective study

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Introduction

During the past 30 years, many studies on *Helicobacter pylori* (*Hp*) and gastroesophageal reflux disease (GERD) have shown that infection with *Hp* is negatively correlated with GERD. Moreover, most scholars appear to believe that *Hp* infection exerts a protective effect on the incidence of GERD.[1–3] The prevalence of *Hp* infection, particularly the *cytotoxin-associated gene A*-positive strain, is significantly lower in patients with GERD than in the general population.[4–6] This is true in East Asia, North America, and Europe, although the prevalence is lowest in East Asians. Some scholars have also shown that *Hp* eradication treatment might increase the incidence of GERD in patients with peptic ulcers (PUs).[7–9] However, one meta-analysis indicated that the eradication of *Hp* was not associated with the incidence of GERD.[10] This point has also been questioned by the 2017 Interpretation of the Fifth Chinese National Consensus Report on Management of *Hp* Infection.[8]

In some studies, *Hp* infection was not associated with the incidence of GERD; however, there is no solid evidence regarding the low prevalence of *Hp* infection in patients with GERD and its so-called "protective" effect. Research of *Hp* and GERD has declined during the last 5 years. The negative correlation between *Hp* and GERD may now be commonly accepted.

PU is the disease condition that is most frequently correlated with *Hp* infection. Nevertheless, no studies to date have reported the association of *Hp*-positive PUs in patients with GERD. The present study was performed to answer the following question: If *Hp* infection actually exerts a protective effect on GERD, is the incidence of GERD lower in patients with than without PUs?

Materials and Methods

In this study, patients with PUs were used as a blank control group. We used logistic regression to analyze the relationship between *Hp* infection and GERD.

This retrospective study included patients who were treated at the Central Hospital of Wuhan from January 2015 to September 2017. The endoscopy findings of the patients and the *Hp* infection status were reviewed using the hospital information system. All patients included in the study were diagnosed with PUs by endoscopy and some by carbon-14 breath testing. Patients with cancer, false-negative results, recent treatment with proton pump inhibitors, treatment by subtotal gastrectomy, and a history of liver disease were excluded.

Gastroscopy was performed by a resident physician with 5 years' experience. The patients were divided into those with PUs, those with GERD (including Barrett's esophagus and reflux esophagitis), and those with PUs combined with GERD according to the gastroscopic diagnosis.

Informed consent was obtained from all patients. The study was approved by the Ethics Committee of the Central Hospital of Wuhan.

Statistical analysis

The statistical analysis was performed using PASW Statistics for Windows, Version 18.0 software (SPSS Inc., Chicago, IL, USA). The *Hp* infection rate were compared between groups using the chi-square test. Multivariate analysis was performed using logistic regression. A P value of <0.05 was considered statistically significant

Results

In total, 2123 patients were diagnosed with PUs by endoscopy (including 1499 who underwent carbon-14 breath testing). After

application of the exclusion criteria, 1431 patients were involved in this study (918 men and 513 women with a mean age of 55.1 ± 12.7 years). Of these 1431 patients, 953 had only PUs (605 men, 348 women; mean age, 55.0 ± 12.3 years), 180 had PUs combined with GERD (152 men, 36 women; mean age, 56.7 ± 13.2 years), and 298 had only GERD (161 men, 137 women; mean age, 54.4 ± 13.5 years). Neither age nor sex had an effect on *Hp* infection [odds ratio (OR), 0.997; 95% confidence interval (CI), 0.986–1.009 and OR, 1.062; 95% CI, 0.800–1.411, respectively].

In total, 36.2% (108/298) of the patients with GERD alone and 75.6% (136/180) of the patients with PU combined with GERD were positive for *Hp* infection, and the difference between these two groups was statistically significant ($P = 0.000$; OR, 5.438; 95% CI, 3.595–8.226) (Table 1).

In total, 67.4% (642/953) of the patients with PUs alone and 75.6% (136/180) of the patients with PUs combined with GERD were positive for *Hp* infection. Among the patients with PUs who were *Hp*-positive, the incidence of GERD was 17.5% (136/778). Among the patients with PUs who were *Hp*-negative, the incidence of GERD was 12.4% (44/355). The difference between these two groups was statistically significant ($P = 0.031$; OR, 1.497; 95% CI. 1.038–2.159). In addition, the probability of developing GERD in patients who were *Hp*-positive was 1.497 times higher than that in patients who were *Hp*-negative. These data are shown in Table 2.

Discussion

In the present study, we found that the prevalence of *Hp* infection in patients with concurrent GERD and PUs was higher than in patients without PUs (75.6% vs. 36.2%, respectively; $P < 0.01$). Moreover, in the analysis of patients with PUs, the rate of *Hp* infection was higher in patients with than without GERD (75.6% vs. 67.4%, respectively; $P = 0.031$). Furthermore, the patients with *Hp*-positive PUs were more likely to develop GERD than were the patients with *Hp*-negative PUs (17.5% vs. 12.4%, respectively; $P = 0.031$).

The incidence of *Hp* infection in patients with GERD is low. Historically, studies have indicated that *Hp* infection might have a protective effect on GERD.[4–7] In more recent years, however, many studies have shown that *Hp* does not have a protective effect on GERD and may have no effects at all. *Hp* has been defined as a class I carcinogen by the World Health

Table 1. Correlation between *Hp* infection and PUs.

Hp	GERD	PUs + GERD	Wald statistic	df	*P*	Exp(B)	95% CI
(+)	108 (36.2)	136 (75.6)	64.289	1	0.000	5.438	3.595–8.226
(−)	190	44					

Hp, *Helicobacter pylori*; PUs, peptic ulcers; GERD, gastroesophageal reflux disease; CI, confidence interval.

Table 2. Correlation between *Hp* infection and GERD.

Hp	PUs	PUs + GERD	Wald statistic	df	*P*	Exp(B)	95% CI
(+)	642 (67.4)	136 (75.6)	4.675	1	0.031	1.497	1.038–2.159
(−)	311	44					

Hp, *Helicobacter pylori*; PUs, peptic ulcers; GERD, gastroesophageal reflux disease; CI, confidence interval.

Organization and is significantly associated with the progression of chronic gastritis, PUs, and gastric cancer. In East Asia, North America, and Europe, however, the prevalence of *Hp* infection is lower in patients with GERD than in healthy controls.[4–6] Raghunath et al.[4] estimated the incidence of *Hp* in patients with and without GERD by a systematic review and showed a lower incidence in patients with GERD. Additionally, case-control studies have shown that *Hp* infection is negatively associated with Barrett's esophagus.[5] These findings indicate that eradication of *Hp* could increase the incidence of GERD. Another study showed that the incidence of reflux esophagitis within 3 years was 25.8% after eradication of *Hp* and 12.9% when the *Hp* infection was ongoing ($P < 0.01$) in the follow-up of patients with duodenal ulcers without reflux esophagitis.[7]

Two studies have shown that *Hp* infection is common in patients with GERD and that *Hp* eradication results in adequate control of GERD symptoms and improves esophagitis.[11,12] Moreover, epidemiologic studies have further supported these data. A large-scale study (approximately 21,000 cases) showed that the decline in the *Hp* infection rate parallels the reduction in PU prevalence and that an increase in GERD and/or reappearance of GERD following *Hp* therapy is rare.[13] One study revealed a low prevalence of *Hp* infection over the long term in a population of Malaysians and showed a low incidence of GERD, Barrett's esophagus, and distal esophageal cancer, signifying that *Hp* infection is not protective against the above-mentioned conditions and that its absence may be beneficial.[14] Patients hospitalized with duodenal ulcers (approximately 61,500 cases) that were apparently attributed to *Hp* infection had a 70% increased risk of esophageal adenocarcinoma.[15] Additionally, *Hp* infection is reportedly associated with GERD, Barrett's esophagus, and esophageal adenocarcinoma.[16] *Hp* has not been reported to be protective against anything, including GERD.[17] The likelihood of metabolic syndrome appears to be significantly increased in relation to *Hp* infection and gastric and duodenal ulcers. These findings suggest that *Hp*-induced long-term gastric inflammation might play a role in metabolic homeostasis.[18,19]

Hp infection might reduce the contractility of the lower esophageal sphincter (LES) by increasing 5-hydroxytryptamine (5-HT) production. Cui et al.[20] evaluated the relationship of *Hp* infection with gastric leptin and found that *Hp* infection increased the gastric leptin levels in the gastric mucosa. Another study by Francois et al.[21] showed that gastric leptin can damage the esophageal mucosa. Ritze et al.[22] found that the 5-HT level was increased through the Janus kinase–signal transducer and activator of transcription-3 pathway, which was activated by increased levels of gastric leptin. Saegusa et al.[23] improved the symptoms of GERD by reducing the levels of 5-HT and increasing the contractility of LES in a GERD mouse model.

Hp is a class of Gram-negative bacilli that is acid-tolerant and microaerobic. It is suitable for growth in environments with oxygen concentrations of 2% to 8%.[24,25] The main cause of GERD is relaxation of the LES, which allows multiple exchanges of air between the stomach and the atmosphere. Hence, GERD can relatively inhibit the growth of *Hp*. Furthermore, patients with *Hp*-positive PUs are more likely to develop GERD than are those with *Hp*-negative PUs. PUs can increase the risk of GERD because of *Hp* infection. In patients with PUs, *Hp* infection is positively associated with GERD. GERD is correlated with a lower *Hp* infection rate, probably because LES relaxation makes it easier for oxygen to enter the stomach, inhibiting the microaerophilic reproduction of *Hp*. Infection by *Hp*

may increase the incidence of GERD by 5-HT, which is impacted by gastric leptin and ghrelin. 5-HT may change the contractility of the LES.

In conclusion, among patients with GERD, the prevalence of *Hp* infection was higher in those with than without PUs. With progression in cell technology, the role of *Hp* will be gradually unveiled. We recognized that the present study has limitations of insufficient characterization of patients and lack of functional studies of *Hp* infection with GERD. Therefore, further studies of the characterization of patients and phenotypes of gastritis are necessary to investigate the pathophysiological mechanisms of *Hp* infection in GERD.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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