

Correlation between *Helicobacter pylori* infection and reflux esophagitis: still an ongoing debate

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Received 14 March 2017

Accepted 11 April 2017

The Egyptian Journal of Internal Medicine
2017, 29:24–29

Context

The vast majority of pathologies in the oesophagus, stomach and duodenum are related to either *H. pylori* infection or gastro-oesophageal reflux disease (GERD). Both conditions affect a large proportion of the population and they may occur either independently or concomitantly. The question of whether the two conditions are mutually exclusive, synergistic, or simply independent is an issue that was raised several years ago and is a matter of ongoing debate.

Aim

We aimed to determine the correlation between gastric *Helicobacter* colonization and grossly and histologically proven reflux esophagitis.

Settings and design

This work was designed as a descriptive cross-sectional study.

Patients and methods

The study was conducted on 50 patients, five women and 45 men, aged 19–79 years (mean: 35.3 years). The inclusion criterion was having a history of symptoms suggestive of GERD.

The cases were chosen from among outpatients and inpatients undergoing diagnostic endoscopic study at the endoscopy unit. The main presenting complaints were GERD symptoms, dyspepsia and postprandial epigastric pain.

All cases were subjected to thorough history taking regarding the details and nature of the presenting complaint, special habits including caffeine consumption, smoking, and intake of medications such as antacids and H₂ blockers, complete physical examination and upper endoscopy.

Detailed description of upper endoscopic examination was reported, including the grade of esophagitis according to Savary–Miller classification.

Three groups of biopsies were taken from each case: the first set from the lower end of the oesophagus and the two other sets from the gastric antrum. The oesophageal biopsies and one set of gastric biopsies were examined histologically after being processed.

The second gastric biopsy set was used for direct detection of *H. pylori* using the rapid urease test (*Campylobacter*-like organism test). The rapid urease test offers a sensitivity of 80–99% and a specificity of 92–100% in untreated patients when compared with histology as the gold standard in the diagnosis of *H. pylori* infection.

Statistical analysis

Data were statistically described in terms of frequencies (number of cases) and percentages and compared using the χ^2 -test. The exact test was used when the expected frequency was less than 5.

Results

On using the rapid urease enzyme test there were 44 (88%) positive cases and six (12%) negative cases for *H. pylori*.

By direct histopathologic examination there were 32 (64%) positive cases and 18 (36%) negative cases for *H. pylori*.

There was no statistically significant correlation between gastric colonization with *H. pylori* and reflux esophagitis diagnosed grossly and histopathologically.

Conclusion

The study showed no statistically significant correlation between *H. pylori* infection and the presence of reflux esophagitis.

Keywords:

H. pylori, reflux esophagitis

Egypt J Intern Med 29:24–29

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1110-7782

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Introduction

Helicobacter pylori infection and gastro-oesophageal reflux disease (GERD) account for most upper gastrointestinal pathologies with a wide spectrum of clinical manifestations.

The interplay of both conditions is complex, in part intriguing, and has become a matter of debate because of conflicting results.

The geographical location, genetic background, ethnicity, gastric location of the infection and bacterial virulence might be strong contributors to the heterogeneity of results in different studies [1].

H. pylori, previously named *Campylobacter pyloridis*, is a Gram-negative, microaerophilic bacterium colonizing the stomach. It was identified in 1982 by Marshall and Warren [2].

GERD is a common condition with a variety of clinical manifestations and potentially serious complications.

The role of *H. pylori* infection in GERD has received attention only recently. However, the evidence for an association between *H. pylori* and GERD is still absent [3].

The objective of this study is to determine the relationship between gastric *Helicobacter* colonization and histologically proven esophagitis.

Patients and methods

The study was conducted on 50 patients, five women and 45 men, aged 19–79 years (mean: 35.3 years). The inclusion criterion was having a history of symptoms suggestive of GERD. The study protocol was approved by the research ethical committee.

Written consent was obtained from all participants.

The cases were chosen from among outpatients and inpatients undergoing diagnostic endoscopic study at the endoscopy unit. The main presenting complaints were GERD symptoms, dyspepsia and postprandial epigastric pain.

All cases were subjected to thorough history taking regarding the details and nature of the presenting complaint, special habits including caffeine consumption, smoking, and intake of medications such as antacids and H₂ blockers, complete physical examination and upper endoscopy.

Detailed description of upper endoscopic examination was reported, including the grade of esophagitis according to Savary–Miller classification [4].

Three groups of biopsies were taken from each case: the first set from the lower end of the oesophagus and the other two sets from the gastric antrum. The oesophageal biopsies and one set of gastric biopsies were examined histologically after being processed.

The second gastric biopsy set was used for direct detection of *H. pylori* using the rapid urease test [*Campylobacter*-like organism (CLO) test]. The rapid urease test offers a sensitivity of 80–99% and a specificity of 92–100% in untreated patients when compared with histology as the gold standard in the diagnosis of *H. pylori* infection [5].

Graded variables in the pathology report included the density of *H. pylori* organisms; inflammation, activity, mucosal atrophy and intestinal metaplasia were reported and graded according to the Sydney system [6].

Each variable was divided into three grades (mild, moderate and severe), and the presence of mononuclear cells was evaluated as well.

H. pylori are visible using haematoxylin and eosin staining but are more easily demonstrated by Giemsa stain. Detection of two or three bacteria per section, if they are absolutely typical of *H. pylori*, is sufficient for diagnosis [7].

Esophagitis is diagnosed by the presence of intraepithelial leucocytes (lymphocytes, neutrophils, eosinophils) and or basal cell hyperplasia. All histological specimens were assessed by a single pathologist who was blinded to the diagnosis of patients.

Data were statistically described in terms of frequencies (number of cases) and percentages and compared using the χ^2 -test. Exact test was used when the expected frequency was less than 5.

Accuracy was represented by sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy.

P values less than 0.05 were considered statistically significant.

All statistical calculations were carried out using IBM Statistical Package for the Social Sciences

(SPSS; IBM Corp, Armonk, New York, USA) release 22 for Microsoft Windows.

Results

- (1) On using the rapid urease enzyme test there were 44 (88%) positive cases and six (12%) negative cases for *H. pylori*.
- (2) By direct histopathologic examination there were 32 (64%) positive cases and 18 (36%) negative cases for *H. pylori*.

There was no statistically significant correlation between gastric colonization with *H. pylori* and reflux esophagitis diagnosed grossly and histopathologically (Tables 1 and 2).

The cases in which the CLO test was positive while the biopsy was negative might be attributed to the following:

- (1) Patients were under treatment with antibiotics.
- (2) The biopsy site was not colonized by *H. pylori*.
- (3) Other *H. pylori*-like organisms may give a false-positive urease enzyme test result.

Discussion

The incidence of *H. pylori* infection in patients with GERD varies widely in the literature – from 30 to 90% – and is ~35% in most series. This heterogeneity among studies may be due to the geographical location of the studies and the virulence of *H. pylori* strains involved [8].

Despite the large number of published studies, the pathophysiological inter-relationship between GERD and *H. pylori* remains controversial.

The pathophysiology of GERD is multifactorial. Although no single factor has been isolated as the

cause of GERD, a negative association between the prevalence of *H. pylori* and the severity of GERD, including Barrett's oesophagus, has been demonstrated in epidemiological studies.

There is considerable heterogeneity among studies, resulting in different conclusions. There are data suggesting a protecting role of *H. pylori* (HP) in GERD, other data suggest an aggravating role, and many studies support a mere coexistence of the two conditions [9].

At present, the relationship between *H. pylori* and GERD is not yet well established, and in the medical literature it is possible to find a variety of reports.

Whereas some authors find a close relationship between both conditions, others do not report any relationship between them, and finally other groups of authors maintain that this micro-organism has even a protective effect against GERD [10].

It has also been postulated that not only the presence of *H. pylori* but also the virulence of each genotype and the anatomic location of the infection with *H. pylori* is important for protection from GERD and its complications. Thus, it has been demonstrated that patients infected by CagA-positive genotypes, which are more virulent, have a lower probability of suffering from GERD and its complications, probably due to a greater degree of atrophic gastritis and hypochlorhydria [1,11–13].

The most widespread opinion now is that there is no consistent relationship between GERD and *H. pylori* infection, although an impact on certain subgroups of patients cannot be entirely ruled out [14].

The aim of our present study is to determine the correlation between gastric colonization with *H.*

Table 1 Correlation of the presence of gastro-oesophageal reflux disease between cases with positive and those with negative *Helicobacter pylori*

GERD	<i>H. pylori</i> positive (n=44)	<i>H. pylori</i> negative (n=6)	P value
Positive	31 (70.45)	4 (66.67)	0.776
Negative	13 (29.55)	2 (33.33)	

GERD, gastro-oesophageal reflux disease; *H. pylori*, *Helicobacter pylori*.

Table 2 Correlation of the presence of esophagitis between cases with positive and those with negative *Helicobacter pylori*

Esophagitis	<i>H. pylori</i> positive (n=44)	<i>H. pylori</i> negative (n=6)	P value
Positive	25 (56.82)	5 (83.33)	0.424
Negative	19 (43.18)	1 (16.67)	

GERD, gastro-oesophageal reflux disease; *H. pylori*, *Helicobacter pylori*.

pylori and grossly and histologically documented reflux esophagitis.

The study was conducted on 50 patients and it was found that 44 (88%) cases were positive for *H. pylori* as per the rapid urease (CLO) test and 32 (64%) cases were positive using direct histopathological examination of gastric biopsies.

There was no statistically significant correlation between esophagitis diagnosed grossly or pathologically with pathologically documented *H. pylori* gastritis.

The results of our study in which we did not find a significant correlation between gastric colonization with *H. pylori* and reflux esophagitis are in accordance with many studies that addressed the same issue.

Manes *et al.* [15] studied 50 patients with GERD (24 HP-positive and 26 HP-negative) using oesophageal manometry and 24-h oesophageal pH-metry.

They concluded that the presence of *H. pylori* has no impact on oesophageal motility, lower oesophageal sphincter pressure, or gastro-oesophageal reflux [15].

The clinical, endoscopic, manometric and pH-metric data in the study of Grande *et al.* [14] show no significant role of *H. pylori* infection in the development of GERD or in the pathogenesis of reflux esophagitis.

Kuipers *et al.* [16] conducted a study on 231 patients to investigate whether *H. pylori* eradication can influence gastritis and its sequelae during long-term omeprazole therapy for GERD.

They found that most *H. pylori*-positive GORD patients have a corpus predominant pangastritis during omeprazole maintenance therapy. Eradication of *H. pylori* eliminated gastric mucosal inflammation and induced regression of corpus glandular atrophy.

H. pylori eradication did not worsen reflux disease, nor did it lead to a need for increased omeprazole maintenance dose. Accordingly, they recommended eradication of *H. pylori* in GORD patients receiving long-term acid suppression [16].

Hong and Kim in 2015 in their meta-analysis concluded a negative association between the prevalence of *H. pylori* and the severity of GERD.

Their explanation was that in patients with East Asian CagA-positive strains, acid injury may be minimized by hypochlorhydria from pangastritis and gastric atrophy. Additionally, host genetic factors may affect the development of GERD [1].

A large-scale prospective cohort study in Korea showed that *H. pylori* infection had a strong negative association with reflux esophagitis and that eradication of *H. pylori* increased the risk for reflux esophagitis [17].

Wu *et al.* [18] conducted a double-blinded placebo-controlled randomized study on 236 patients to investigate the effects of *H. pylori* eradication on treating GERD patients.

Their final conclusion showed that *H. pylori* eradication rendered the control of reflux disease more difficult. However, balancing the risk for gastric carcinogenesis and peptic ulcer formation against the need for higher doses of acid suppressive therapy for symptom control, they recommended *H. pylori* eradication before long-term PPI therapy [18].

Awad *et al.* [19] studied 37 patients with GERD (78% HP-positive) using ambulatory 24-h oesophageal pH-metry and manometry. There was no difference in the manometric findings between HP-positive and HP-negative groups but the HP-positive patients had a lower acid exposure tendency.

This may suggest a protective role of HP in the pathogenesis of GERD [19].

A recent study explored this debate from a different perspective through the hypothesis of altered motility induced by *H. pylori* infection. That study aimed to explore the effects of *H. pylori* infection on both motilin and ghrelin.

The study concluded that *H. pylori* infection is neither protective nor harmful with respect to gastro-oesophageal reflux and neither ghrelin nor motilin levels were associated with gastro-oesophageal reflux. Neither gastrin, ghrelin, or motilin levels were affected by *H. pylori* infection. There is an inverse association between gastrin and ghrelin levels after *H. pylori* eradication [11].

Perhaps the importance of finding an answer to the debate on the relation between *H. pylori* infection

and reflux esophagitis is the conclusion of Iijima *et al.* [20], who addressed the importance of eradicating HP by stating that eradication will suppress gastric inflammation and inhibit gastric mucosal atrophy, which would subsequently stop the progression to intestinal metaplasia and development of gastric cancer.

In their study, Iijima *et al.* [20] noticed that reflux esophagitis occurred in ~10% of Japanese patients undergoing eradication therapy.

Accordingly, the fact that eradication-induced reflux esophagitis could increase the long-term risk for Barrett's oesophagus and oesophageal adenocarcinoma should also be considered in the Japanese population.

They recommended appropriate treatment with proton pump inhibitors for patients undergoing eradication therapy in clinical practice.

Conclusion

Our study did not show a correlation between *H. pylori* infection and presence of GERD. Accordingly, it can be assumed that infection with *H. pylori* is not related to the pathogenesis of GERD. However, it needs to be emphasized that as there are multiple factors determining the complex interaction between *H. pylori* and reflux esophagitis, and bearing in mind that geographical location and ethnicity as well as genetic factors are strong contributors to the heterogeneity of results in different studies, and as no large-scale study has addressed this complex interaction in the Egyptian population, no solid conclusions can be drawn from the initial results of our study because of the small sample size, and further prospective nationwide large-scale studies are needed.

Another reason for the need to conduct large-scale studies in Egypt addressing the complex inter-relationship between *H. pylori* infection and GERD are the recent epidemiologic data in western countries that documented that the prevalence of GERD and oesophageal adenocarcinoma has increased as the prevalence of *H. pylori* has decreased.

According to these epidemiologic findings in western countries it is believed that eradicating *H. pylori* might provoke reflux esophagitis with its consequences, namely Barrett's oesophagus and subsequent development of oesophageal adenocarcinoma [21].

Accordingly, wide-scale studies need to be conducted in Egypt for follow-up of cases after eradicating *H. pylori* infection and to determine whether or not reflux will increase, because if such a hypothesis is correct in the Egyptian population it means that all patients in whom *H. pylori* had been eradicated need to be followed up closely.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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