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Relationship between Helicobacter Pylori infection and Gastro-esophageal Reflux Disease

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ABSTRACT

Background:According to research, eradication of Helicobacter Pylori (Hp) infection may be followed by development of Gastro-Esophageal Reflux Disease (GERD), there has been concern regarding the interactions between Hp and GERD.
Aim: This study aims to investigate the relationship between Helicobacter Pylori (H. pylori), and oesophagitis (non-erosive or erosive) in patients with reflux symptoms.
Material and method: A total of 50 patients, fulfilling the inclusion criteria, were enrolled after taking informed consent. Endoscopy (and/or non-invasive tests like stool antigen test SAT, Serology: Non-invasive) was performed in all patients. On endoscopy, focusing on severity of esophagitis, either non-erosive or erosive esophagitis. During endoscopy, tissue biopsies were obtained for histopathology, which were then forwarded to the pathology lab for H. pylori detection.
Results: Out of the total of 50 individuals, males were 21(42%) and females were 29(58%). The mean age of the study population was 36.01+7.41 (ranged 15-65) years. H. Pylori was reported in 15(30%) cases, signifying that 35(70%) of GERD cases were H. Pylori negative. Out of a total of 50 participants, the endoscopic findings revealed Non Erosive Reflux Disease (NERD) in 42(84%) cases and Erosive Esophagitis in 8(16%) cases. H. Pylori was positive in 3(20%) of erosive esophagitis patients and in 12(80 %) of NERD patients, (P< 0.3).
Conclusion: The present study concluded that H. Pylori was present in 30% cases of GERD. Out of which, non-erosive reflux disease was associated with a greater frequency of helicobacter infection. Overall, the patients having GERD are more probable to have non-erosive reflux disease versus erosive esophagitis on endoscopy**.**

Keywords: *Gastro-esophageal reflux disease (GERD), H. pylori (Hp), Non Erosive Reflux Disease (NERD), Erosive Esophagitis (EE).*

INTRODUCTION

Gastro-esophageal reflux disease is a common disorder characterised by abnormal exposure of the oesophageal mucosa to acidic gastric contents. This may cause symptoms or mucosal damage, or both, of variable severity.1

Since the observation by Labenz et al1, that eradication of Helicobacter pylori (Hp) infection may be followed by development of reflux esophagitis in a relevant proportion of patients previously not affected by gastro esophageal reflux disease (GERD), there has been concern regarding the interactions between Hp and GERD.

H. pylori, as the most commonly prevalent and recognized bacterium, is carried by more than half of the world population. Once colonized, H. pylori induces a persistent, but superficial, inflammation, resulting in duodenal ulcer, gastric ulcer, and gastric cancer. 2

The global prevalence of H pylori infection has declined during the last 3 decades in adults. 3

Epidemiological studies have now demonstrated that the prevalence of peptic ulcer disease and gastric (distal) cancer is falling, in parallel with a falling prevalence of Hp infection in the western countries. While the prevalence of GERD is steadily increasing in the developed countries, as is the incidence of adenocarcinoma of the esophagus, its most dangerous complication. Suggesting that H pylori has a role in these diseases. 4

Currently, we have no clear data to show that patients with GERD are more frequently infected by H pylori than controls. Instead, a study has pointed to a protective role of H. pylori in the pathogenesis of esophagitis. A study by Li A, et al, showed that risk of reflux oesophagitis (RE) occurrence or recurrence significantly increased after eradication of H. pylori.[6.]

This supports the earlier observation by Labenz et al.

On the other hand, a study by Jonaitis et al, showed that there is no evidence indicating that H. pylori eradication could worsen the symptoms or the course of GERD.[7]

The issue that is still debated is: How does Hp infection interfere with the pathogenesis of GERD?

① Mechanisms by which H pylori might *protect* against GERD: H pylori infection may lower intragastric acidity as H pylori generates large amounts of ammonia which has a high pKa of 9.1 and acts as a powerful neutralising substance at elevated gastric pH.[1] Patients harboring the H pylori, may be protected if the infection involves the corpus (i.e. the acid-producing part of the gastric mucosa), because the amount of acid secretion and hence the esophageal acid exposure is reduced.[8] Others have hypothesized that in some patients with HP, the organism colonizes the antrum preferentially, resulting in an antrum-dominant gastritis characterized by aggravated GERD symptoms and increased gastrin and acid secretion. HP eradication reduced acid secretion.[11] Supporting this, a case-control study from Korea that is a nation with high prevalence of atrophic gastritis-showed the association between H.pylori seropositivity and a reduced risk for erosive esophagitis.[9]

②Mechanisms by which H pylori might *contribute* to the development of GERD: H pylori gastritis is accompanied by the release of numerous mediators, cytokines and nitric oxide which may adversely affect the lower esophageal sphincter and possibly promote an inflammatory response in, and mucosal damage to, the adjacent oesophageal mucosa. Also, H pylori infection leads to increased production of prostaglandins which, in addition to inflammatory mediators, can sensitise afferent nerves and reduce LOS pressure.[1] A defective anti-reflux barrier is probably responsible for macroscopically detectable injury to the esophageal squamous epithelium, which results in erosive esophagitis. However, more than 70% of patients that experience heartburn do not have visible lesions at endoscopy and they are termed as NERD (Non Erosive Reflux Disease).[9]

As GERD is influenced by multiple risk factors—such as body mass index, smoking, lifestyle habits, and host-related factors—establishing a definitive relationship between the Hp and GERD remains challenging.[9]

As H. pylori forges the stomach homeostasis inducing inflammation using proinflammatory cytokines, it influences the activity of somatostatin-producing D cells, gastrin-producing G cells, and acid-producing parietal cells.[9]

Gastrin, the major hormonal stimulant for acid secretion, is synthesized in pyloric mucosal G cells. It binds to gastrin/CCK2 receptors on parietal and, more importantly, histamine-containing enterochromaffin-like (ECL) cells, to induce acid secretion. Gastrin is also a trophic hormone that maintains the integrity of gastric mucosa, induces proliferation of parietal and ECL cells, and is thought to play a role in carcinogenesis. Somatostatin, present in D cells of the gastric pyloric and oxyntic mucosa, is the main inhibitor of acid secretion, particularly during the interdigestive period.[10]

H. pylori gastritis causes a reduction in somatostatin levels and, since somatostatin negatively regulates gastrin, hypergastrinemia ensues. Gastrin is a specific growth factor for H. pylori, so this potentially creates a positive-feedback loop. If not detected or cured, the bacterium or H. pylori continues its proliferation and inflammation of gastric mucosa causing the progressive loss of gastric glands. The atrophic changes markedly increase risk of gastric ulceration and non-cardia gastric adenocarcinoma but the lower acid production protects against duodenal ulceration, and probably against acid-induced complications of gastroesophageal reflux.[9]

Early HP eradication reduces the occurrence of gastroduodenal ulcer and carcinoma. However, there is no consensus on the effects of HP eradication on GERD, and the mechanisms are still not entirely known. There are no unified standards for the application of anti-HP therapy in GERD patients. However, eradication of HP is recommended in the guidelines of the Italian Society of Gastroenterology and guidelines of Japan (Kato et al., 2019; Romano et al., 2022). Other explanations show that HP eradication has a beneficial effect on GERD (Miwa et al., 2002).[11]

Wang H, et al, did a systematic review with a comprehensive literature search in the databases, for the associations of H. pylori infection with GERD risk in prospective studies. A total of 25 eligible studies were included. Their study suggested that H. pylori infection is associated with a decreased risk of GERD.[12]

The present study was undertaken to determine the prevalence of H. pylori infection in GERD and to evaluate the occurrence of non-erosive reflux disease (NERD) and erosive esophagitis (EE), among affected patients, in our resource poor area.

Material and method: The present descriptive cross sectional study was conducted at the department of General Medicine, Unit III, Bolan Medical Complex Hospital, Quetta from January 2020 to June 2025, after taking permissions. Individuals of both genders and of different age groups, who had visited the unit with symptoms of gastro-esophageal reflux disease including, retrosternal burning pain, epigastric pain, more frequent symptoms at night, and acid reflux into the mouth, for longer than two weeks were included in this study, while individuals on proton pump inhibitors, those taking aspirin or NSAIDS, having co-morbid condition and those who had previously had Helicobacter pylori therapy were excluded.

Informed consent were taken from each participant. The participants underwent endoscopy (and/or non-invasive tests like stool antigen test SAT, Serology: non-invasive) which were performed in all patients. On endoscopy, focus was on severity (non-erosive or erosive) of esophagitis and tissue biopsies were taken from each subject. To identify H. Pylori, specimens were sent to Pathology Lab. Collected data was analyzed through SPSS version 24.

For continuous variables like age, basic descriptive statistics were given, such as a mean and standard deviation. Examples of categorical variables that were characterized using percentages and frequencies were H pylori, GERD, and NERD. The Chi square X^2 test was used to examine the prevalence of infection with H. pylori in individuals with GERD and NERD. P values were deemed significant if they were less than 0.05.

Results: A total of 50 individuals were enrolled in this study out of which males were 21(42%) and females were 29(58%). The mean age of the study population was 36.01+7.41 (ranged15-65) years. H. Pylori was reported in 15(30%) cases, signifying that 35(70%) of GERD cases were H. Pylori negative. Out of a total of 50 participants, the endoscopic findings revealed Non Erosive Reflux Disease (NERD) in 42(84%) cases and Erosive Esophagitis (EE) in 8(16%) cases, as presented in **Table 1.**

Table 1. Distribution by Gender, Age, Endoscopic Results, and H. Pylori

Variables	**Frequency /percentage**
H.pylori	
Present	15(30%)
Absent	35(70%)
Endoscopic findings	
Erosive Esophagitis	8(16%)
Non Erosive Reflux Disease	42(84%)
Gender	
Male	21(42%)
Female	29(58%)
Age in years (Mean + SD)	36.01+7.41 ranged(15-65)
Age categories	
15 to 40	33(66%)
41 to 65	17(34%)

Age wise, participants were categorized, in younger individuals (15–40 years old) and older individuals (41–65 years old), and GERD was present in 66% and 34%, respectively. In younger individuals (15–40 years old) erosive esophagitis was seen in 2(6%), while in older (41-65 years old) individuals it was seen in 3(17.6), (p = 0.4). Gender wise, NERD was recorded in 24(82.7%) female individuals and in male it was 18(85.7%) (p= 0.047). Similarly Erosive Esophagitis was reported in 5(17.2%) female and 3(14.2%) male. NERD was not only the commonest (82%) cause of GERD, but NERD was also common in both H.pylori positive 12(80. %) and H.pylori negative 30(85.7%) cases (p <0.3) (80. % versus 85.1%), as presented in **Table 2.**

Table 2. Endoscopic Results according to Age, Gender, & H. Pylori Status

	Endoscopic results		
	Erosive Esophagitis	NERD	**P value**
H .pyori			**0.3**
Positive 15	3(20%)	12(80. %)	
Negative 35	5(14.2%)	30(85.7%)	
Gender			0.047
Male	3(14.2%)	18(85.7%)	
Female	5(17.2%)	24(82.7%)	
Age			0.40
15-40	2(6%)	31(93.9%)	
41-65	3(17.6%)	14(82.3%)	

DISCUSSION

Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder that leads to the regurgitation of gastric contents into the esophagus. GERD significantly impacts the economy and quality of life. GERD can be triggered by intrinsic and/or structural mechanisms that break the barrier of esophago-gastric junctions, the esophagus exposed to acidic contents of the stomach. Heartburn, regurgitation, chest discomfort, tooth erosions, persistent cough, asthma, and laryngitis are all symptoms.[13]

GERD can be classified into three main categories: the first one is non-erosive reflux disease (NERD), the second is erosive esophagitis (EE), and the last one is Barrett esophagus (BE). The most prevalent condition is NERD, while EE occur in 30% and BE occur in between 6% and 12% of patients. While lifestyle changes and medications like the proton pump inhibitor (PPI) are commonly used to treat GERD, medically resistant GERD has become more prevalent. [14]

With regional fluctuation, the overall frequency of GERD symptoms is roughly 13%. With nearly 25%, South Asia and Southeast Europe have the highest incidence, whereas the lowest is found in the Southeast Asian region, Canada, and France. [15]

Currently, there are various diagnostic methods used for H. pylori infection in different subjects, but the only methods with both high sensitivity and high specificity remain useful and recommendable. According to a traditional classification, H. pylori infection can be diagnosed by *noninvasive* tests such as H. pylori antigen in stool specimen, UBT (Urea Breath Test), serology, and *invasive* tests such as PCR (polymerase chain reaction), culture, and histology which require endoscopic surgery and biopsy specimens. Disparate distribution (patchy) of H. pylori in stomach is causing the bias in sampling (false negative). Indeed, taking a biopsy specimen (maximally 3-4 mm^2) cannot guarantee the existence of H. pylori-colonized in stomach environment (500–1000 mm^2 in different persons). A solution would be to increase the number of taken gastric biopsies, but for ethical limitations, gastroenterologists are highly prohibited to take 6 or more biopsies from a patient. Lastly, endoscopy is an impossible procedure for subjects such as pregnant women, children, and elderly patients. An overview (of a few) of H. pylori diagnosis with invasive and noninvasive methods are: [16]

Serology: noninvasive

Sensitivity: >96%. Specificity: 60–90%Advantage: Has no false negative result.

Disadvantage: Failure to distinguish between active and past infection. (IgA-based measurement was also suggested but noted that the test is less trustful and reliable than IgG-based assays)

SAT: (stool antigen test), Noninvasive

Sensitivity: >95%. Specificity: >95%

Advantage: High specificity and sensitivity. Good popularity among patients. Relatively fast and simple. No need of skilled staff.

Histology: Invasive

Sensitivity: 60–90%. Specificity: >95%

Advantage: The gold standard for direct H. pylori detection

Disadvantage: The relatively high rate of false negative reports. [16]

In our study to detect the presence of H.pylori, the participants underwent invasive (endoscopic biopsy) as well as non-invasive tests like stool antigen test SAT and Serology (non-invasive).

In the our study of GERD, 58% of patients were females. This female predominance in GERD, has been seen in many studies. It has been seen that the risk factors for GERD include female gender, smoking, genetic predisposition. [17]

The mean age of our present study's population was 36.01+7.4 years. Other studies have shown varying findings. The mean age was 42.95 in study by Niknam R et al's [18] study. They however concluded that except for sociodemographic status ($P < 0.001$), other variables including gender, age, ethnicity, body mass index (BMI), smoking, and presence of hiatus hernia in patients had no significant association with the frequency of H. pylori infection.[18]

In the present study, H. Pylori was reported in 30% cases, signifying that 70% of GERD cases were H. Pylori negative. NERD was not only the commonest (82%) cause of GERD, but NERD was also common in 80% H.pylori positive patients. H.pylori was positive in 20% of Erosive Esophagitis (EE) patients. These findings are inline with another study done in Pakistan[19] on 150 GERD patients, which revealed that 13.3% (20) of the patients had erosive esophagitis, while 86.7% (130) had non-erosive reflux illness. H. Pylori was positive in 42(28%) patients, out of which, 38(90.5%) had NERD, while 4(9.5%) had EE. This signified that 108(72%) patients of GERD patients were Hp negative.[19] The results of this study are similar our study, which may probably be due to the fact that both studies were done in the same country. The fact supporting this is, that a study done by Gatopoulou A,[20] et al, performed prospectively on a series of 50 patients with reflux symptoms, revealed that the overall prevalence of H pylori+ was 70%.[20]

In the research by Niknam et al,[18] the H. pylori infection was diagnosed in 77% patients in the GERD group. H.pylori was detected in 77.6% patients in mild GERD patients (LA grade A and B), while lesser number of cases of severe GERD (LA grade C and D) were positive for H. pylori infection. These findings were consistent with our study findings that H.pylori was positive in 80% of cases of non-erosive reflux disease, while H.pylori was found in 20% of cases of erosive esophagitis.

In the current study, NERD was observed in 85.7% of female patients and 82.7% of male patients. Erosive esophagitis was identified in 17.2% of females and 14.2% of males. NERD was more prevalent than erosive esophagitis in both H. pylori–positive and H. pylori–negative individuals (80.1% vs. 85%). These results align with the findings of Niknam et al.[18]

In a study on the relationship between Helicobacter pylori infection and gastroesophageal reflux disease, by Yılmaz S, et al[21], H. pylori, which was detected in 75% of the GERD patients. The relationship between the presence of H. pylori and *gender* revealed that among the H. pylori-positive patients, 75% of the females were infected with H. pylori, but results were not statistically significant.[21] Their study findings are consistent with our study findings in that in our study the majority of GERD cases were females, but different in the aspect that in our study H.pylori was positive in 30% of GERD cases. The study by Yılmaz S, et al,[21] showed that there was no significant relationship between the presence and degree of reflux oesophagitis and H.pylori infection. Chronic inflammation and neutrophil activity were higher in the antrum and corpus in the H. pylori-positive group, and gland atrophy was detected more frequently in the antrum in the H. pylori-negative group. Concluding that the histological type of gastritis caused by H. pylori rather than the presence of H. pylori may be associated with GERD.

An interesting research by Salman Al Gharbawi H et al,[22] done to determine the prevalence of H. pylori infection in patients with erosive and non-erosive gastro-esophageal reflux disease included a total of 54 patients. This is similar to our research in the topic as well as the number of patients. Salman Al Gharbawi H,[22] et al, graded the severity of GERD by SAVARY – MILLER classification, and patients were grouped into 4 groups: (Group A = non-erosive GERD) (Group B = erosive GERD) (Group C = symptoms with negative endoscopy) (Group D = control). The inclusion of control gave their study an added dimension. But in our study we used only two groups for the severity of GERD , non-erosive & erosive esophagitis. Salman Al Gharbawi H, et al, found H. pylori infection was positive in 14 patients (73.6%) in Group A = non-erosive GERD, while it was positive in 6 patients (24 %) in group B= erosive GERD , 7 patients (70%) in group C = symptoms with negative endoscopy, and 5 patients (50%) in group D= control.[22] These findings are similar to our study in that, in non-erosive GERD, H.pylori was positive in 80%. While in erosive esophagitis, H.pylori was positive in 20% of cases in our study. Concluding that in both studies Helicobacter pylori prevalence is higher in patients having non-erosive GERD as compared to patients with erosive GERD.

Another study was performed prospectively in 50 patients with reflux symptoms by Gatopoulou A, et al. Esophageal erosions were found during endoscopy in 21 of these patients. The overall prevalence of H pylori+ was 70% (erosive: 15/21, 71.5%; non-erosive: 20/29, 68.9%). [19]

Ashktorab H, et al, in their research showed that the frequency of HP positivity in esophagitis patients was 4 % and in normal controls 34 %. These results show H. pylori has a significant negative association with esophagitis in African Americans

which may point to a protective role of H. pylori in the pathogenesis of esophagitis.[23]

The reason of difference between the results of these studies can be multifactorial. As different researches have shown that with regional fluctuation, the overall frequency of GERD varies from country to country. The overall frequency of GERD symptoms is roughly 13%. With nearly 25%, South Asia and Southeast Europe have the highest incidence, whereas the lowest is found in the Southeast Asian region, Canada, and France.[15]

Another factor which may account for varying results in H. pylori and GERD prevalence results in different researches is that GERD is also influenced by other risk factors including age, BMI, low socioeconomic status, tobacco use, alcohol consumption, connective tissue disorders, postprandial supination, and various drugs.[24]

Untreated GERD can progress to serious consequences. Persistent acid reflux can lead to Barrett's esophagus, an intestinal metaplasia resulting from acid exposure. This disorder causes the typical squamous cell epithelium to be replaced with columnar epithelium, including goblet cells, which can develop into esophageal adenocarcinoma; hence, early discovery is critical for prevention and care. [25]

CONCLUSION

The present study concluded that non-erosive reflux disease is associated with a greater frequency of helicobacter infection ($P < 0.3$), and individuals with GERD are more probable to have non-erosive reflux disease versus erosive esophagitis on endoscopy. Further studies are recommended..

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