Gastroesophageal Reflux Disease and *Helicobacter pylori*: What May Be the Relationship?

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Relationship between *Helicobacter pylori* (*H. pylori*) and gastroesophageal reflux disease (GERD) is controversial. We aimed to review the possible relationship between *H. pylori* infection and GERD. Epidemiological data indicate an inverse relationship between frequency of *H. pylori* infection and prevalence of GERD and its complications like Barrett's esophagus and esophageal adenocarcinoma. *H. pylori* eradication in patients with peptic ulcer disease may be associated with increased risk of development of GERD compared with untreated patients. Infection with cagA bearing strains of *H. pylori* was associated with less severe GERD including endoscopic esophagitis, possibly due to pangastritis leading to hypochlorhydria. Recent studies on inflammatory markers (IL-1β and IL-1RN) suggest pro-inflammatory genotypes to be protective against development of severe GERD, especially in patients with *H. pylori* infection. Identification of candidate genes playing an important role in gastric acid secretion and visceral hypersensitivity to the esophageal epithelium might help in early detection of individuals susceptible to develop GERD. Interplay between *H. pylori* and host factors play an important role in the pathogenesis of GERD.

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Key Words
Esophagitis, Gastric acid, Gastritis, Genes

Introduction

Gastroesophageal reflux disease (GERD) is a common condition, often associated with impairment in health-related quality of life. Esophageal acid exposure in patients with GERD may be severe enough to cause endoscopically visible mucosal damage (erosive esophagitis), which is graded by Los Angeles classification, peptic esophageal stricture, and Barrett’s esophagus (BE). In a good proportion of patients, there is no endoscopically visible mucosal damage of esophageal mucosa in spite of symptoms of GERD and esophageal acid exposure. This condition is termed as endoscopy-negative reflux disease (ENRD). Recent reports indicate ENRD to be quite common all over the world.

Several factors may influence the severity of GERD. Esophageal acid exposure not only depends on reflux of gastric contents into esophagus and failure of esophagus to clear it by peristaltic contractions but also on pH of the refluxed gastric juice. pH of gastric juice depends on acid secretory capacity of oxyntic or parietal cells. *Helicobacter pylori* (*H. pylori*) infection is common in many parts of the world. Since GERD is also a com-
mon condition, co-existence of this disease and H. pylori infection is quite expected. What could be the relationship between H. pylori infection and occurrence and severity of GERD? Most studies suggest that H. pylori may protect against development of GERD or may reduce its severity,6-9 however, a few studies do suggest that it may aggravate GERD.10,11 Supportive evidences discussed below will elucidate the possible relationship between GERD and H. pylori.

Epidemiological Studies Regarding the Relationship Between GERD and H. pylori Infection

Frequency of H. pylori infection is lower in people from developed countries such as North America, Western Europe and Australia12-14 whereas that of GERD and its complications are more frequent among them.15-17 In contrast, frequency of H. pylori infection is higher in people from developing nations such as South America, Eastern Europe, Africa, China and India16-22 while that of GERD and its severity is lower among them.19,23-26 Furthermore, there is decline in incidence of peptic ulcer disease and distal gastric carcinoma globally but increase in GERD and its complications such as BE and esophageal adenocarcinoma (EAC).6,27,28 Moreover, frequency of H. pylori infection is also decreasing worldwide due to better hygiene and increasing use of antibiotics.29 Therefore, one can assume a possible negative relation between H. pylori infection and frequency and severity of GERD.

Asian perspective

Asian data also support an inverse relationship between GERD and its complications and H. pylori infection. Data from Korea showed that prevalence of reflux esophagitis was 7.9% and majority of patients had mild grades of disease (Los Angeles classification A and B),30 and frequency of BE was low (0.84%).31 A study from China suggested that the prevalence of erosive esophagitis and BE was 4.3% and 1.0%, respectively and H. pylori was negatively associated with erosive esophagitis.32 One of the reasons for increase in prevalence of GERD in Japan in recent years is thought to be due to decrease in H. pylori infection rate33 and absence of H. pylori infection was one of the risk factors for occurrence of GERD in another study.34 Hence, most studies suggest a possible protective role of H. pylori against GERD.

Evidences From H. pylori Eradication Studies

It is well-established that eradication of H. pylori heals peptic ulcer and prevents its recurrence. Increased severity of GERD and its complications such as BE after successful eradication of H. pylori in patients with or without peptic ulcer has been documented in several studies.7,8,35-37 Others reported de novo development or exacerbation of GERD after treatment of H. pylori38,39 particularly among Asians compared to North Americans and Europeans.40 Development of GERD following eradication of H. pylori may reflect an increase in the acidity of the refluxate superimposed on pre-existing abnormalities in gastroesophageal motility. Conversely, some studies did show beneficial effect of H. pylori eradication on symptoms of GERD.41,42

In a meta-analysis by Yaghoobi et al,43 though frequency of GERD was not found to be higher after eradication of H. pylori among dyspeptic patients, there was two folds increased risk of its development with successful eradication among patients with peptic ulcer compared to untreated controls. What could be the explanation for this? It is possible that the dyspeptic patients already had irreversible reduction in gastric acid secretion due to pangastritis in contrast to those with peptic ulcer, who are known to have increased parietal cell mass causing hyperchlorhydria. This meta-analysis therefore, may suggest a possible protective role of H. pylori infection against the development of GERD at least among patients with peptic ulcer.

Asian perspective

Data from Asia on this issue is scant. A study from Japan showed improvement in pre-existing reflux esophagitis after H. pylori eradication in patients with GERD associated with duodenal ulcer.44 These results are contradictory to most other studies. Fujiwara explained the mechanism of such results as follows: (1) normalization of gastric acidity in patients with duodenal ulcer might play an important role, (2) secondly, heartburn and/or acid regurgitation might be confused with symptoms of peptic ulcer disease; hence, the symptoms might be felt as improved after the cure of H. pylori infection and (3) lastly, if peptic ulcer itself directly or indirectly induced GERD, healing of the ulcer might result in improvement of GERD.35 Hence, patients having GERD with peptic ulcer were benefited by the H. pylori eradication therapy. Furthermore, in Japan H. pylori should be eradicated in patients with GERD as well due to high incidence of gastric cancer.45
Mechanism of Gastric Acid Alteration by *H. pylori* and Its Relationship With GERD

*H. pylori* infection leads to gastritis that might alter gastric acid secretion. The degree and extent of gastritis may be related to host genetic or agent (*H. pylori* strains) factors.

1. *H. pylori*, gastritis and gastric acid secretion altering GERD severity

*H. pylori* may influence gastric acid secretion in 2 ways: (1) limited inflammation in the gastric antrum is associated with destruction of somatostatin secreting D-cells. Thus, there is loss of negative feedback on gastric acid secretion resulting in increased parietal cell mass and hyperchlorhydria, which may increase severity of GERD and (2) pangastritis (more often associated with cytotoxin-associated gene A [cagA] and vacuolating cytotoxin [VacAs1] bearing strains) leads to destruction of acid secreting parietal cells of gastric corpus, causing gastric atrophy with consequent hypochlorhydria (Fig. 1); this may reduce the severity of GERD and its complications. A review by Sharma and Vakil also suggested a negative association between the prevalence of *H. pylori* infection especially cagA bearing strains and BE and EAC.

A study from Taiwan showed that only 33% of 276 patients with reflux esophagitis had *H. pylori* infection compared with 67.5% of 378 with normal esophagus. Triple virulent (cagA, blood-group antigen-binding adhesion gene [babA2] and vacAs1a) genotype of *H. pylori* was also uncommon among patients with reflux esophagitis. In a study from Hong Kong, the prevalence of *H. pylori* infection among 225 patients with GERD was 34%; *H. pylori* infected patients had less severe esophagitis than those without it. Of those infected with *H. pylori*, 70%, 76% and 78% of ENRD, erosive esophagitis and control subjects, respectively were cagA positive. Protective effect of cagA positive strains of *H. pylori* against GERD has also been shown in Iran. Another multi-ethnic study from Malaysia suggested that cagA-positive strains of *H. pylori* was associated with reduced severity of GERD among Indians. As prevalence of cagA bearing strains of *H. pylori* is high in some developing countries, frequent occurrence of hypochlorhydria may protect against development of severe GERD and its complications in these areas of the world.

2. Endoscopic severity of GERD and *H. pylori* infection

Patients with severe GERD (higher Los Angeles grades) are less often infected with *H. pylori*. Also, cagA bearing strains of *H. pylori* is more frequent in patients with ENRD than those with esophageal reflux disease and its sequel, suggesting the protective role of these strains of bacteria against development of severe GERD.

**Host Factors**

Final outcome following exposure to a disease-causing agent is also influenced by the host factors. Not only the environmental

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**Figure 1.** Possible role of various factors including *H. pylori* in pathogenesis of gastroesophageal reflux disease.
or dietary factors, but host physiological as well as genetic factors may play important role in the pathogenesis of GERD. Role of host physiological factors, such as hypertensive lower esophageal sphincter, transient lower esophageal sphincter relaxations, delayed gastric emptying, presence of hiatus hernia, hyperperistalsis of esophagus are well established in pathogenesis of GERD. However, there is still inadequate literature on host genetic factors, which may influence development of GERD. Also, the clearance of *H. pylori* may be related to host genetic factors in addition to differences between strains.

Importance of the genetic factors in GERD is supported by recent reports that showed that there is increased concordance for GERD in monozygotic twin pairs as compared to dizygotic pairs, indicating genetic rather than shared environmental effect. Limited studies have shown that IL-1B-511C allele, IL-1B-31T allele, G protein beta 3 subunit 825T allele, IL-1RN + 2018 allele, IL-1B-511C allele, IL-1B-31T allele, 2/2 genotype of IL-10-1082, homozygous extensive of CYP2C19, homozygous variant of Xeroderma pigmentosum complementary group C poly (AT) insertion/deletion polymorphism gene are the potential risk factors for either GERD or its complications such as BE and EAC.

**Possible Molecular Mechanisms**

1. **H. pylori and gastric acid alteration**

   *H. pylori* infection induces a substantial inflammatory reaction in the gastric mucosa with recruitment of leukocytes and over-expression and release of pro-inflammatory cytokines. This inflammation may be due to the secreted proteins from *H. pylori*, which initiate a cascade of signaling events within the host cells resulting in up regulation of several inflammatory mediators. Various bacterial factors, which may reduce gastric acid secretion and thereby severity of GERD are as follows: (1) VacA, especially the virulent form s1m1, inhibits gastric acid secretion by disrupting the apical membrane-cytoskeletal interaction in gastric parietal cells: this may reduce esophageal acid exposure; (2) bacterial lipopolysaccharides reduces gastric acid secretion through prostaglandin system and by inhibition of H⁺/K⁺-ATPase enzymatic function or changes in cytoskeletal rearrangements in H⁺/K⁺-ATPase subunits rather than by down-regulation of transcriptional or translational events; (3) CagA protein, encoded by cagA gene, is a part of cag pathogenicity island. This is translocated into the host cells by Type-IV secretion apparatus. Once translocated, it undergoes tyrosine phosphorylation at the Glu-Pro-Ile-Tyr-Ala motif. The presence of a single Glu-Pro-Ile-Tyr-Ala motif is necessary for the membrane localization of CagA. CagA injection into the host gastric epithelial cell can induce NF-κB activation and IL-8 production. Thus, infection with *cag* positive strains may lead to more inflammation in the stomach, causing hypochlorhydria; (4) Other *H. pylori* proteins, such as outer membrane inflammatory protein, is considered to be important in stimulation of IL-8 secretion, even in *cag*-negative strains, though to a much lesser extent and (5) *H. pylori* neutrophil activating protein can induce neutrophils to produce reactive oxygen radicals damaging gastric epithelium.

2. **Genetic factors in susceptibility to GERD**

   Limited studies have shown that host genetic factors that may influence development of GERD include genes, which may alter gastric acid secretion (pro and anti-inflammatory factors and those involved in acid secretory pathway), DNA repair pathway (for BE and EAC), cancer detoxification pathway (for EAC), cell cycle regulatory pathway and visceral hypersensitivity to the refluxed acid in esophagus (Fig. 1). Recently, visceral hypersensitivity has been shown to be involved in the pathogenesis of GERD. Patients with GERD may have normal esophageal acid exposure, but their esophageal mucosa can be more sensitive to the acid reflux, leading to heartburn and erosive esophagitis due to visceral neural pathway dysfunction. It is also elucidated that one of the major reasons for heartburn among patients with ENRD may be related to esophageal visceral hypersensitivity. A recent study revealed role of host genetic polymorphism of G-protein beta 3 subunit gene (G-protein-coupled receptors intervene the response to acid, neurotransmitters and humoral factors transforming esophageal sensory function) in the enhanced perception of reflux events. However, more research is needed on several other candidate genes, which could be potentially involved in the above mentioned pathways.

In summary, infection with *H. pylori* may lead to gastric inflammatory response, which could be either antral or corpus, depending on the *H. pylori* strain and host genetic and environmental factors.
3. Interplay of host genetic factors, *H. pylori* and intestinal helminthes

Since *H. pylori* is an extra-cellular organism, a Th2-cell response (IL-4, IL-5, IL-10, IL-13 and TGF-β) would favor the host to clear the bacteria and prevent occurrence of chronic infection. Paradoxically, *H. pylori*-specific gastric mucosal T cells generally present a Th1 phenotype (IFN-γ, IFN-β, TNF, IL-2 and IL-1β cell mediated immune response). It has been shown that infection with intestinal helminthes induces Th2-associated IgG1 responses to *H. pylori* infection. Hence, intestinal helminthes infection may clear the infection by promoting Th2-polarizing immune responses to *H. pylori*. Some of these cytokine polymorphisms have been shown to affect the degree of gastritis.

In developing nations, prevalence of *H. pylori* infection as well as that of helminthes is high because of poor hygienic conditions. If an individual gets an infection with helminthes first, they will have Th2 predominant cytokine profile, hence preventing persistent *H. pylori* colonization. On the other hand, if an individual has concomitant infection with *H. pylori* and helminthes (the possibility of which is more common), they might show an intermediate Th1 and Th2 cytokine profile. Thus, a balance between Th1 and Th2 responses may be important in degree of persistence of *H. pylori* infection. This might decide the degree of gastric inflammation and hence, the severity of GERD.

*H. pylori* infection also activates expression of chemokines such as IL-8 and Gro-α. But, their expression is dependent on the corresponding expression of their receptors (CXCR1 and CXCR2) on neutrophils. IL-8 may influence development of gastritis and duodenal ulcer in patients with *H. pylori* infection.

Possible role of other factors such as Gro-α, monocyte chemoattractant protein-1 (MCP-1) and CXCR1 and CXCR2 receptors in pathogenesis of *H. pylori* infection and GERD can be studied. These molecular mechanisms suggest a complex interplay between various host factors, agent and environmental factors, which decides the final outcome of the disease.

**Conclusion**

Most epidemiological as well as eradication studies suggest a possible protective role of *H. pylori* infection against GERD. Recent data on the role of host genetic factors suggest possible mechanism of influence of *H. pylori* in the pathogenesis of GERD. Latest studies targeting the role of inflammatory markers (IL-1β and IL-1RN) suggest that presence of the pro-inflammatory genotypes are associated with less severe GERD. Polymorphism studies on genes for visceral hypersensitivity, GNB3 also supports that patients with GERD experience enhanced perception of reflux events. Hence, interplay between both agent (*H. pylori*) as well as host factors play an important role in the pathogenesis of GERD.

Study of role of host genetic factors in the pathogenesis of GERD will be the major thrust area for research in near future, as there is scanty data on it. Identification of candidate genes playing role in gastric acid secretion and visceral hypersensitivity to the esophageal epithelium might help in early detection of individuals susceptible to develop GERD. Furthermore, simultaneous study of these genetic polymorphisms with *H. pylori* infection, dietary and life style factors such as obesity, presence of gall stones, smoking, and conditions like chronic laryngitis and chronic obstructive pulmonary disease, which are known to be associated with GERD, would be important in evaluating their combined effect on risk of GERD. This may help to undertake preventive strategies for individuals at risk through life style changes.

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Gastroesophageal Reflux Disease and Helicobacter pylori

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