**Review Article**

*Helicobacter pylori* Infection in Gastroesophageal Reflux Disease in the Asian Countries

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*Helicobacter pylori* infection, a common infection in many countries, is related to the clinical course of upper gastrointestinal diseases. Gastroesophageal reflux disease (GERD) is a common esophageal disease in Western countries and its prevalence is increasing in Asian countries. 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 esophagus, has been demonstrated in epidemiological studies. The high prevalence of *H. pylori* infection affects the incidence of GERD in Asian countries. In the subjects 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. The interactions between genetic factors and the virulence of *H. pylori* infection may be the reason for the low prevalence of GERD in Asian countries.

*H. pylori* eradication is not considered pivotal in GERD exacerbation based on evidence from Western studies. A recent meta-analysis demonstrated that eradication therapy of *H. pylori* was related to a higher risk of developing *de novo* GERD in Asian studies. *H. pylori* infection remains an inconclusive and important issue in GERD in Asian countries.

1. Introduction

The prevalence of gastroesophageal reflux disease (GERD) in the general population has been estimated to be 10–20% [1–4]. Conversely, most Asian population-based studies have reported a lower prevalence of less than 10% [3–6]. In epidemiological studies, *H. pylori* and GERD have been found to be negatively associated and strongly related to cytotoxin-associated gene product- (CagA-) positive strains of *H. pylori* [7]. However, an increasing prevalence of GERD and decreasing prevalence of *H. pylori* have been reported in Asian countries [8], which is in agreement with a previous report of no increase in the prevalence of GERD symptoms with age [4]. GERD markedly reduces patients’ quality of life and imparts a significant economic burden on the healthcare system [9–11]. Therefore, decreasing the prevalence of *H. pylori* infection is an important issue in GERD, especially in Asian populations. In addition, *H. pylori* eradication has been presumed to exacerbate GERD due to improvement of gastritis and the recovery of hypochlorhydria; several studies have been conducted to clarify this controversy.

2. Gastric Acidity and *H. pylori*

Gastric acid plays a key role in the etiology of GERD and is an element of the disease that may be modified by *H. pylori* infection. Gastric secretion can increase, decrease, or remain steady depending on the pattern of *H. pylori*-related inflammation [12]. The major components of acid secretion in patients with *H. pylori* infection include the density of *H. pylori* colonization, its distribution, and the severity of the mucosal inflammatory response to the infection. Patients with a duodenal ulcer and *H. pylori* infection have antrum-predominant gastritis, which leads to hypergastrinemia and
3. Epidemiological Evidence of a Link between H. pylori Infection and GERD

Table 1 shows recent epidemiological reports of an inverse relationship between H. pylori infection and reflux esophagitis or Barrett’s esophagus in the western countries and East Asian countries [30–35]. This negative association was also evident in patients with severe GERD and H. pylori infection with virulent CagA-positive strains in Western countries [36, 37]. The prevalence of H. pylori infection is inversely correlated with the risk and severity of reflux esophagitis; [30, 37, 38] and the prevalence of H. pylori infection suggests a protective role in both Barrett’s esophagus and esophageal adenocarcinoma [7, 34, 35, 37–41].

4. Proton Pump Inhibitors (PPIs) in GERD Patients with H. pylori Infection

Long-term maintenance therapy of proton pump inhibitors (PPIs) for GERD induces gastritis and progression of gastric atrophy and intestinal metaplasia to gastric adenocarcinoma in patients with H. pylori infection [46, 47]. These patterns are significantly associated with the CagA-positive strains [48]. Current guidelines, including the Asia-Pacific Consensus for H. pylori infection, recommend H. pylori eradication in GERD patients requiring long-term PPIs [49]. However, there is no evidence that H. pylori eradication reduces the risk of gastric adenocarcinoma in patients with this condition.

5. H. pylori Eradication in GERD

Despite the inverse relationship between H. pylori and GERD in cross-sectional studies, the results are less consistent in prospective studies of H. pylori eradication in patients with GERD. Early studies revealed that H. pylori eradication was positively associated with reflux esophagitis or GERD symptoms in patients with gastric and duodenal ulcer diseases [50, 51]. Hiatal hernia, corpus gastritis, and CagA-positive H. pylori strains have been reported to be risk factors for newly developed reflux esophagitis after H. pylori eradication [51, 52]. However, other studies have shown improvement of reflux symptoms after H. pylori eradication in patients with peptic ulcer disease and nonulcer dyspepsia [53, 54]. The Maastricht IV Consensus Report suggested that H. pylori eradication does not exacerbate preexisting GERD or affect treatment efficacy [55]. A recent meta-analysis demonstrated that eradication therapy of H. pylori was related to a significantly higher risk of developing de novo GERD in Asian studies [42]. In contrast, no such risk has been reported by Western studies [43–45]. Table 2 shows the summaries of the results of meta-analyses. However, this remains an inconclusive issue in Asian countries. For example, two large-scale cohort studies in Korea produced inconsistent results [56, 57]. Thus, the revised version of the Korean guidelines for Helicobacter pylori infection states that H. pylori eradication does not affect the development or clinical course of GERD [58].

6. Conclusion

H. pylori infection and GERD are highly prevalent conditions globally. The prevalence of H. pylori varies geographically and among ethnicities. Many epidemiological studies have shown a negative correlation between H. pylori infection and GERD. A specific virulence factor, such as CagA, and specific host genotypes may affect the diverse prevalence and other aspects of GERD owing to individual differences in acid secretion. A high prevalence of CagA-positive strains has been reported in Asian countries. The diversity of H. pylori infection between Western and Asian countries should be considered when
Table 1: Recent epidemiologic studies for association between *Helicobacter pylori* infection and GERD.

| Study [references] | Type of study | Location     | Number of cases in each group (𝑛) | H. pylori infection assessments | H. pylori prevalence (%) in each group |
|--------------------|---------------|--------------|-----------------------------------|-------------------------------|---------------------------------------|
| Chunget al. 2011 [30] | Case-control  | Korea        | Reflux esophagitis (2,808) Control (2,808) | Serology                      | Reflux esophagitis (38.4) Control (58.2) |
| Gunji et al. 2011 [31] | Cross-sectional | Japan       | Erosive esophagitis (1,831) No erosive esophagitis (8,009) | Serology                       | Erosive esophagitis (13.6) No erosive esophagitis (33.4) |
| Chiba et al. 2012 [32] | Cross-sectional | Japan       | Erosive esophagitis (728) No erosive esophagitis (4,262) | Serology                       | Erosive esophagitis (9.4) No erosive esophagitis (14.9) |
| Ashktorab et al. 2012 [33] | Case-control  | USA          | Reflux esophagitis (58) Gastritis (1,558) Reflux esophagitis and gastritis (363) Normal control (41) | Biopsy silver stain or immunohistochemistry | Reflux esophagitis (3.8) Gastritis (40) Reflux esophagitis and gastritis (34) Normal control (34) |
| Sonnenberg et al. 2010 [34] | Cross-sectional | USA         | Barrett’s esophagus (2,510) No Barrett’s esophagus (76,475) | Biopsy immunohistochemistry    | Barrett’s esophagus (5.7) No Barrett’s esophagus (12.2) |
| Thrift et al. 2012 [35] | Case-control  | Australia    | Simple Barrett’s esophagus (217) Dysplastic Barrett’s esophagus (95) Control (398) | Serology                       | Simple Barrett’s esophagus (12) Dysplastic Barrett’s esophagus (3) Control (18) |

GERD: gastroesophageal reflux disease.

Table 2: Results of meta-analyses for *Helicobacter pylori* eradication on GERD.

| Study [references] | Number of enrolled studies | Location of enrolled studies | Risk ratio (95% confidence interval) | Conclusion |
|--------------------|----------------------------|-----------------------------|--------------------------------------|------------|
| Xie et al. 2013 [42] | 12 cohort studies and 12 RCTs | Cohort Europe: 4 North America: 1 Asia: 7 RCTs Europe: 7 South America: 1 Asia: 4 | 3 type A cohort studies: 2.50 (1.46–4.26, 𝑃 = 0.0008) 9 type B cohort studies: 1.70 (1.30–2.23, 𝑃 = 0.0001) 12 RCTs: 1.09 (1.23–3.22, 𝑃 = 0.005) 4 Asian RCTs: 4.53 (1.66–12.36, 𝑃 = 0.003) | Eradication of the infection may be a risk factor for *de novo* endoscopic GERD, especially in Asian populations. |
| Yaghoobi et al. 2010 [43] | 5 cohort studies and 7 RCTs | Cohort Europe: 1 Asia: 4 RCTs Europe: 3 North America: 3 South America: 1 | 5 cohort studies: 1.37 (0.89–2.12, 𝑃 = 0.15) 6 RCTs using erosive GERD as outcome: 1.11 (0.81–1.53, 𝑃 = 0.52) 5 RCTs using symptomatic GERD as outcome: 1.22 (0.89–1.69, 𝑃 = 0.22) | There is no association between *H. pylori* eradication and development of new cases of GERD in the population of dyspeptic patients. |
| Qian et al. 2011 [44] | 11 RCTs | Europe: 5 North America: 3 South America: 1 Asia: 1 Multinational: 1 | 7 RCTs using heartburn symptom as outcome: 0.88 (0.63–1.23, 𝑃 = 0.46) 10 RCTs using erosive esophagitis as outcome: 0.97 (0.67–1.40, 𝑃 = 0.88) | *H. pylori* eradication does not aggravate the clinical outcomes in terms of short-term and long-term post eradication occurrence of GERD. |
| Saad et al. 2012 [45] | 10 RCTs | Europe: 7 North America: 2 Asia: 1 | 10 RCTs using symptomatic GERD as outcome: 0.81 (0.56–1.71, 𝑃 = 0.27) 10 RCTs using endoscopic esophagitis as outcome: 1.13 (0.72–1.78, 𝑃 = 0.59) | Treatment of *H. pylori* does not seem to increase GERD symptoms or reflux esophagitis. However, documented eradication of *H. pylori* appears to significantly improve GERD symptoms. |

RCT: randomized controlled trial; GERD: gastroesophageal reflux disease; *H. pylori*: Helicobacter pylori.
analyzing the results of studies of *H. pylori* eradication in GERD patients. To date, cohort studies and randomized controlled trials of the effects of *H. pylori* eradication on GERD are inconclusive. The decreasing prevalence of *H. pylori* and the recovery of acid secretion capacity after eradication in patients with CagA-positive *H. pylori* and corpus gastritis are possible causes of the higher prevalence of GERD in Asian countries. These issues necessitate a more detailed study.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**Authors’ Contribution**

Su Jin Hong wrote the paper; Sang Woo Kim revised the paper.

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