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REVIEW ARTICLE

Does *Helicobacter pylori* infection protect against esophageal diseases in Asia?

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Abstract The speculations on the protective role of *Helicobacter pylori* against gastroesophageal reflux disease (GERD) originated from epidemiological observations. These studies have shown that the rising trend of GERD is coincident with declining prevalence of *H. pylori* and peptic ulcer disease in Asia. Furthermore, most case–control and population-based studies suggest a negative association between *H. pylori* infection and GERD. It is generally believed that the preponderance of cagA+ and vacA+ virulent strains and proinflammatory interleukin-1 beta polymorphism increase the risk of hypochlohydria and protects against the development of GERD in Asian population. Recovery of gastric acid secretion and emergence of reflux esophagitis has been reported after *H. pylori* eradication in patients with corpus gastritis and atrophic gastritis. Recent studies have also reported that *H. pylori* eradication leads to recovery of ghrelin secreting cells in the gastric corpus and a rise in plasma ghrelin levels, which may contribute to obesity through its appetite-stimulating action and predispose to GERD. The prevalence of *H. pylori* infection is generally lower in younger Asians who enjoy improved socioeconomic status and sanitation compared with their older counterparts. The Asian population is probably facing a rising generation with high gastric acid and ghrelin secretion rates. These physiological changes may contribute to increased dietary calorie intake, obesity and increased prevalence of GERD.

Keywords Asian · Gastroesophageal reflux disease · Obesity

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Introduction

Gastroesophageal reflux disease (GERD) has been one of the commonest upper gastrointestinal disorders in the Western countries, with reported prevalence of about 10% to 20%. On the other hand, most Asian population based studies reported a much lower prevalence of less than 10% [1–8]. Most patients with reflux esophagitis in Asia have mild erosive esophagitis. Barrett's esophagus and esophageal adenocarcinoma are rare [5, 9–14].

While there is a large discrepancy in prevalence and severity of GERD, another major difference in the epidemiology of acid peptic disorders between eastern and Asian populations is the prevalence of *Helicobacter pylori* and its related diseases. *H. pylori* infection and peptic ulcer diseases are significantly more common in Asian population. Gastric cancer, which is strongly associated with *H. pylori*, is common in East Asian countries such as China and Japan. As a result, these opposing epidemiological observations lead to the speculations that *H. pylori* may protect against the development of GERD in Asian population.

This review aimed to address the possible protective role of *H. pylori* against GERD from different perspectives, which included epidemiological relationships, biological plausibility and longitudinal post-eradication studies.

Opposing secular trends of *H. pylori* related diseases and GERD

There is an opposite trend, globally, of the incidence of *H. pylori* related diseases and GERD. In the western countries, hospitalization and mortality rates for peptic ulcer and gastric cancer had dropped substantially from 1970 and 1995, while hospitalisation rates for GERD and esophageal adenocarcinoma rose significantly [15]. In Asia, similar rising trend of symptomatic GERD, endoscopic esophagitis and even esophageal adenocarcinoma has been observed in many retrospective endoscopy-based studies, and these changes in prevalence were coincident with a decline in prevalence of *H. pylori* infection, peptic ulcer and gastric cancers [16–20].

Negative association between *H. pylori* and GERD in cross-sectional studies

Most case–control and population-based studies tend to suggest a negative association between *H. pylori* infection and GERD in Asia. The prevalence of *H. pylori* infection in GERD patients ranges 25% to 35%, which is 25% to 40% lower than that of the "non-reflux" population in Asia [21, 22]. On the other hand, this negative association is only confined to patients with severe GERD in Western countries, especially for those infected by more virulent cagA+ strains [23, 24]. The association of *H. pylori* infection with reduced risk for esophageal adenocarcinoma is independent of confounding environmental and genetic modifiers such as smoking and IL-1β or TNF-alpha polymorphism, suggesting a genuine independent negative relationship between *H. pylori* and GERD [25].

Prevalence of *H. pylori* is also inversely related to severity of GERD. The prevalence of *H. pylori* in patients ranges 20% to 33% for esophagitis, and 0% to 37% for Barrett's esophagus. Furthermore, patients with reflux esophagitis have lower rates of virulent *H. pylori* infection compared to non-reflux controls. [12, 26, 27].

Putative protective mechanisms of *H. pylori* against GERD

Inflammation of the gastric mucosa induced by *H. pylori* infection and its resultant dysfunction of gastric acid secretion has been considered the most important putative mechanism that accounts for the protective role of *H. pylori* against GERD [28–31]. Patients with duodenal ulcer have antrum-predominant pattern of *H. pylori* gastritis, which leads to hypergastrinemia and acid hypersecretion. On the other hand, patients with gastric ulcer and gastric cancer are characterized by corpus-predominant gastritis or pangastritis, which is associated with profound destruction or even atrophy of acid-secreting mucosa. These patients are characterized by gastric acid hyposecretion, and eradication of *H. pylori* is followed by rebound gastric acid hypersecretion in this group of patients. Recovery of gastric acid secretion and emergence of reflux esophagitis after *H. pylori* eradication have been reported in patients with corpus gastritis and atrophic gastritis [32–34]. It has been shown that GERD patients with *H. pylori* infection have more severe esophageal dysmotility and lower esophageal sphincter dysfunction, suggesting that the protective acid-reducing effect of *H. pylori* is offset by severe esophageal dysmotility in the pathogenesis of GERD [35].

Bacterial virulence and host inflammatory response are the two major determinants of gastric inflammation and acid secreting pattern. CagA+ and vacA+ virulent strains account for more than 70% of infected Asian population and pro-inflammatory interleukin-1 beta polymorphism. This increases the risk of hypochlohydria and protects against reflux esophagitis and may also be more prevalent in Asia. Because of the high prevalence of the virulent strain and abundance of pro-inflammatory haplotypes of interleukin-1 beta polymorphism, there is probably a higher proportion of gastric acid hyposecretors among Asians infected by *H. pylori*. This may account for the strong negative association between *H. pylori* and GERD in Asia that is not apparent in western countries [36–39].

In recent years, it has been increasingly recognized that *H. pylori* eradication may affect gastric secretory functions other than acid secretion. The plasma level of ghrelin, a strong appetite-stimulating hormone that is produced in the gastric corpus, is lower in *H. pylori*-infected patients compared to healthy controls. *H. pylori* eradication leads to recovery of ghrelin secreting cells and increase in plasma ghrelin levels [40–42]. This might increase the calorie intake and lead to weight gain. While there is no positive relationship between plasma ghrelin level and risk of GERD complications, the strong association between GERD and obesity has been extensively reported. Recent studies also support a similar "dose–response" association between GERD and BMI in Asians. Patients with reflux esophagitis tend to have higher BMI compared to non-erosive reflux disease patients and non-reflux controls [11, 43–45]. There is still a lack of evidence that the decline in *H. pylori* infection has contributed to high levels of ghrelin and increased calorie intake in Asian population. However, there is no doubt that the rising problem of obesity is one of the major contributing factors for an increasing prevalence of GERD in Asia.

Risk of emergence of GERD after *H. pylori* eradication

Despite the negative association between *H. pylori* and GERD observed in cross-sectional studies, the results are less consistent in longitudinal studies of *H. pylori* eradication. These conflicting observations may be attributed to ethnic variation and the different dominant patterns of *H. pylori* gastritis between peptic ulcer and non-ulcer patients.

Most longitudinal studies were conducted in western population. In a meta-analysis of pooled data from 7 randomized controlled trials and 5 cohort studies comparing the prevalence of GERD among patients free from GERD at baseline with *H. pylori* eradication vs. those with persistent infection, there was no significant difference in either the risk of developing erosive or symptomatic GERD between the two groups of patients. There was no significant heterogeneity among the studies and the results were consistent in various subgroup and sensitivity analyses, suggesting high quality and consistency. Interestingly, there was a two-fold higher risk of development of erosive GERD in a subgroup of patients with peptic ulcer disease in cohort studies (odds ratio: 2.04, 95% C.I.: 1.08–3.85; $p=0.03$) [46]. Yet, the findings of this meta-analysis may not be applicable in Asian population.

Compared to studies from western countries, recent studies from Asia have reported an increased risk of GERD after *H. pylori* eradication in both peptic ulcer patients and healthy, non-reflux participants of endoscopy screening project. In a cohort study of median follow up period of 2 years in 4,007 healthy screening subjects in South Korea, there was no significant association between emergence of reflux symptoms and *H. pylori* eradication. On the other hand, the risk of erosive esophagitis increased significantly after *H. pylori* eradication (OR 2.34; 95% CI, 1.45–3.76; $p<0.001$) and was comparable to that of the *H. pylori*-negative group [47].

In another prospective cohort study of 1,187 Japanese *H. pylori*-positive patients with peptic ulcer diseases who were confirmed not to have esophagitis at baseline, reflux esophagitis was significantly more prevalent (27.9% vs. 13.9% among those with persistent infection) in patients who had cure of infection after a mean follow up period of 3.6 years. However, the esophagitis was mild in most patients and 50% of these patients only had transient esophagitis and only 4% required maintenance therapy [48].

How can these conflicting results be reconciled? While there is no doubt that there is a global inverse secular trend and most cross-sectional studies suggest a negative association between *H. pylori* and GERD, there is substantial ethnic heterogeneity between Asian and Western populations. Moreover, the effect size of *H. pylori* eradication on the risk of GERD is probably too small to be detected in randomized controlled trials or cohort studies of small sample size and short follow up period. Current evidence also suggests that the risk of developing severe GERD de novo after *H. pylori* eradication is low in the intermediate period of time. Post-eradication GERD is likely mild and transient with little long term clinical relevance.

Conclusion

The changing dynamics of various risk and protective factors have led to an increased prevalence and severity of GERD in Asia [49]. Decline in *H. pylori* infection and the widespread practice of *H. pylori* eradication may have direct impacts on the pattern and spectrum of acid peptic disorders in this part of the world. The prevalence of *H. pylori* infection is generally lower in younger Asians who enjoy improved socioeconomic status and sanitation compared with their older community members. Hence, most Asian populations are probably facing a rise in the proportion of individuals with high gastric acid and ghrelin secretion rates. These physiological changes may contribute to increased dietary calorie intake, obesity and emergence of GERD.

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References

1. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005;54:710–7.
2. Kang JY. Systematic review: geographical and ethnic differences in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2004;20:705–17.
3. Fujiwara Y, Higuchi K, Watanabe Y, et al. Prevalence of gastroesophageal reflux disease and gastroesophageal reflux disease symptoms in Japan. J Gastroenterol Hepatol. 2005;20:26–9.
4. Ho KY, Kang JY, Seow A. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. Am J Gastroenterol. 1998;93:1816–22.
5. Kim N, Lee SW, Cho SI, et al. The prevalence of and risk factors for erosive oesophagitis and non-erosive reflux disease: a nationwide multicentre prospective study in Korea. Aliment Pharmacol Ther. 2008;27:173–85.
6. Wong WM, Lai KC, Lam KF, et al. Prevalence, clinical spectrum and health care utilization of gastro-oesophageal reflux disease in a Chinese population: a population-based study. Aliment Pharmacol Ther. 2003;18:595–604.
7. Yang SY, Lee OY, Bak YT, et al. Prevalence of gastroesophageal reflux disease symptoms and uninvestigated dyspepsia in Korea: a population-based study. Dig Dis Sci. 2008;53:188–93.

8. Li Z, Zou D, Ma X, et al. Epidemiology of peptic ulcer disease: endoscopic results of the systematic investigation of gastrointestinal disease in China. Am J Gastroenterol. 2010;105:2570–7.
9. Chang CS, Poon SK, Lien HC, Chen GH. The incidence of reflux esophagitis among the Chinese. Am J Gastroenterol. 1997;92:668–71.
10. Lee SJ, Song CW, Jeen YT, et al. Prevalence of endoscopic reflux esophagitis among Koreans. J Gastroenterol Hepatol. 2001;16:373–6.
11. Tseng PH, Lee YC, Chiu HM, et al. Prevalence and clinical characteristics of Barrett's esophagus in a Chinese general population. J Clin Gastroenterol. 2008;42:1074–9.
12. Wu JC, Sung JJ, Chan FK, et al. Helicobacter pylori infection is associated with milder gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000;14:427–32.
13. Yeh C, Hsu CT, Ho AS, Sampliner RE, Fass R. Erosive esophagitis and Barrett's esophagus in Taiwan: a higher frequency than expected. Dig Dis Sci. 1997;42:702–6.
14. Rosaida MS, Goh KL. Gastro-oesophageal reflux disease, reflux oesophagitis and non-erosive reflux disease in a multiracial Asian population: a prospective, endoscopy based study. Eur J Gastroenterol Hepatol. 2004;16:495–501.
15. el-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. Gut. 1998;43:327–33.
16. Fernandes ML, Seow A, Chan YH, Khek-Yu H. Opposing trends in incidence of esophageal squamous cell carcinoma and adenocarcinoma in a multi-ethnic asian country. Am J Gastroenterol. 2006;101:1430–6.
17. Sollano JD, Wong SN, ndal-Gamutan T, et al. Erosive esophagitis in the Philippines: a comparison between two time periods. J Gastroenterol Hepatol. 2007;22:1650–5.
18. Goh KL, Wong HT, Lim CH, Rosaida MS. Time trends in peptic ulcer, erosive reflux oesophagitis, gastric and oesophageal cancers in a multiracial Asian population. Aliment Pharmacol Ther. 2009;29:774–80.
19. Ho KY, Chan YH, Kang JY. Increasing trend of reflux esophagitis and decreasing trend of Helicobacter pylori infection in patients from a multiethnic Asian country. Am J Gastroenterol. 2005;100:1923–8.
20. Lim SL, Goh WT, Lee JM, Ng TP, Ho KY. Changing prevalence of gastroesophageal reflux with changing time: longitudinal study in an Asian population. J Gastroenterol Hepatol. 2005;20:995–1001.
21. Haruma K, Hamada H, Mihara M, et al. Negative association between Helicobacter pylori infection and reflux esophagitis in older patients: case-control study in Japan. Helicobacter. 2000;5:24–9.
22. Wu JC, Sung JJ, Ng EK, et al. Prevalence and distribution of Helicobacter pylori in gastroesophageal reflux disease: a study from the East. Am J Gastroenterol. 1999;94:1790–4.
23. Vicari JJ, Peek RM, Falk GW, et al. The seroprevalence of cagA-positive Helicobacter pylori strains in the spectrum of gastroesophageal reflux disease. Gastroenterology. 1998;115:50–7.
24. Weston AP, Badr AS, Topalovski M, Cherian R, Dixon A, Hassanein RS. Prospective evaluation of the prevalence of gastric Helicobacter pylori infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. Am J Gastroenterol. 2000;95:387–94.
25. Whiteman DC, Parmar P, Fahey P, et al. Association of Helicobacter pylori infection with reduced risk for esophageal cancer is independent of environmental and genetic modifiers. Gastroenterology. 2010;139:73–83.
26. Lai CH, Poon SK, Chen YC, Chang CS, Wang WC. Lower prevalence of Helicobacter pylori infection with vacAs1a, cagA-positive, and babA2-positive genotype in erosive reflux esophagitis disease. Helicobacter. 2005;10:577–85.
27. Zhang J, Chen XL, Wang KM, Guo XD, Zuo AL, Gong J. Relationship of gastric Helicobacter pylori infection to Barrett's esophagus and gastro-esophageal reflux disease in Chinese. World J Gastroenterol. 2004;10:672–5.
28. Abe Y, Ohara S, Koike T, et al. The prevalence of Helicobacter pylori infection and the status of gastric acid secretion in patients with Barrett's esophagus in Japan. Am J Gastroenterol. 2004;99:1213–21.
29. Anderson LA, Murphy SJ, Johnston BT, et al. Relationship between Helicobacter pylori infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut. 2008;57:734–9.
30. Yamamori K, Fujiwara Y, Shiba M, et al. Prevalence of symptomatic gastro-oesophageal reflux disease in Japanese patients with peptic ulcer disease after eradication of Helicobacter pylori infection. Aliment Pharmacol Ther. 2004;20:107–11.
31. Chourasia D, Misra A, Tripathi S, Krishnani N, Ghoshal UC. Patients with Helicobacter pylori infection have less severe gastroesophageal reflux disease: a study using endoscopy, 24-hour gastric and esophageal pH metry. Indian J Gastroenterol. 2011;30:12–21.
32. Koike T, Ohara S, Sekine H, et al. Helicobacter pylori infection inhibits reflux esophagitis by inducing atrophic gastritis. Am J Gastroenterol. 1999;94:3468–72.
33. Koike T, Ohara S, Sekine H, et al. Helicobacter pylori infection prevents erosive reflux oesophagitis by decreasing gastric acid secretion. Gut. 2001;49:330–4.
34. Koike T, Ohara S, Sekine H, et al. Increased gastric acid secretion after Helicobacter pylori eradication may be a factor for developing reflux oesophagitis. Aliment Pharmacol Ther. 2001;15:813–20.
35. Wu JC, Lai AC, Wong SK, Chan FK, Leung WK, Sung JJ. Dysfunction of oesophageal motility in Helicobacter pylori-infected patients with reflux oesophagitis. Aliment Pharmacol Ther. 2001;15:1913–9.
36. Ando T, El-Omar EM, Goto Y, et al. Interleukin 1B proinflammatory genotypes protect against gastro-oesophageal reflux disease through induction of corpus atrophy. Gut. 2006;55:158–64.
37. Kato S, Onda M, Yamada S, Matsuda N, Tokunaga A, Matsukura N. Association of the interleukin-1 beta genetic polymorphism and gastric cancer risk in Japanese. J Gastroenterol. 2001;36:696–9.
38. Queiroz DM, Guerra JB, Rocha GA, et al. IL1B and IL1RN polymorphic genes and Helicobacter pylori cagA strains decrease the risk of reflux esophagitis. Gastroenterology. 2004;127:73–9.
39. Chourasia D, Achyut BR, Tripathi S, Mittal B, Mittal RD, Ghoshal UC. Genotypic and functional roles of IL-1B and IL-1RN on the risk of gastroesophageal reflux disease: the presence of IL-1B-511*T/IL-1RN*1 (T1) haplotype may protect against the disease. Am J Gastroenterol. 2009;104:2704–13.
40. Isomoto H, Nakazato M, Ueno H, et al. Low plasma ghrelin levels in patients with Helicobacter pylori-associated gastritis. Am J Med. 2004;117:429–32.
41. Nwokolo CU, Freshwater DA, O'Hare P, Randeva HS. Plasma ghrelin following cure of Helicobacter pylori. Gut. 2003;52:637–40.
42. Tatsuguchi A, Miyake K, Gudis K, et al. Effect of Helicobacter pylori infection on ghrelin expression in human gastric mucosa. Am J Gastroenterol. 2004;99:2121–7.
43. Moki F, Kusano M, Mizuide M, et al. Association between reflux oesophagitis and features of the metabolic syndrome in Japan. Aliment Pharmacol Ther. 2007;26:1069–75.
44. de MC, Haggerty TD, Corley DA, Vogelman JH, Orentreich N, Parsonnet J. Serum ghrelin levels and risk of subsequent adenocarcinoma of the esophagus. Am J Gastroenterol. 2007;102:1166–72.

45. Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ. Obesity is associated with increased transient lower esophageal sphincter relaxation. Gastroenterology. 2007;132:883–9.
46. Yaghoobi M, Farrokhyar F, Yuan Y, Hunt RH. Is there an increased risk of GERD after Helicobacter pylori eradication?: a meta-analysis. Am J Gastroenterol. 2010;105:1007–13.
47. Nam SY, Choi IJ, Ryu KH, Kim BC, Kim CG, Nam BH. Effect of Helicobacter pylori infection and its eradication on reflux esophagitis and reflux symptoms. Am J Gastroenterol. 2010;105:2153–62.
48. Take S, Mizuno M, Ishiki K, et al. Helicobacter pylori eradication may induce de novo, but transient and mild, reflux esophagitis: prospective endoscopic evaluation. J Gastroenterol Hepatol. 2009;24:107–13.
49. Ghoshal UC, Chourasia D. Gastroesophageal reflux disease and Helicobacter pylori: what may be the relationship? J Neurogastroenterol Motil. 2010;16:243–50.