

# Gastroesophageal reflux disease at the turn of *millennium*

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## Abstract

Gastroesophageal reflux disease (GERD) has been an area of active research in the Asia-Pacific region in the recent years. This article outlines some of the interesting research findings. It comprises three parts. The first part dealt with recent data on the changing epidemiology of GERD in Asia. The second part summarized published studies on the relationship between GERD and *Helicobacter pylori*, relevant to the Asia-Pacific region. The last part discussed some of the recent advances in the treatment of GERD.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) has been an area of dynamic research in the Asia Pacific region in the last few years. This article outlines some of the interesting research findings.

## CHANGING EPIDEMIOLOGY OF GERD IN THE ASIA PACIFIC REGION

There was little information on GERD in the Asia Pacific region until recently. A cross-sectional survey of randomly selected adults in Singapore provided evidence that reflux-type symptoms were uncommon in the Asian population in the early 90's<sup>[1]</sup>. Of 700 persons evaluated, only 2 % reported having heartburn more than once a month. A similar study among a random sample of 5 000 adult residents in Shanghai and Beijing showed a point prevalence of symptomatic GERD of 6 %<sup>[2]</sup>.

These prevalence rates were lower than those of Western populations. Endoscopic esophagitis was also less common among Asians than their Western counterparts. One of the evidences came from a comparative study of consecutive English patients and Singaporean patients seen for upper abdominal discomfort<sup>[3]</sup>. Reflux *esophagitis* was found in 25 % of the English patients and only 6 % of the Singaporean patients ( $P<0.005$ ). The most important risk factor for *esophagitis* was race. An endoscopic study conducted among 16 606 patients in Southern China supported the Singaporean finding, showing a similarly low frequency of endoscopic esophagitis of 4 %<sup>[4]</sup>. It also showed that esophagitis, when present, was often mild with the vast majority of cases being Los Angeles grade A or B. Severe esophagitis and large hiatal hernia were rare in Asians.

In the past few years, there has been an increase in the frequency of GERD in Asia. In a re-survey<sup>[5]</sup> of community

residents who were interviewed in an earlier study in 1994<sup>[1]</sup>, there was a more than 4-fold increase in the frequency of heartburn. This trend could not be explained by genetic factors *per se*. It also did not appear to be related to lifestyle changes such as smoking, alcohol consumption, or changes in body weight. Among a consecutive series of 9 000 patients who had diagnostic esophagogastroduodenoscopy, the frequency of endoscopic *esophagitis* was also increasing ( $P<0.001$ ) while that of duodenal ulcer was decreasing ( $P<0.005$ ), from 1992 to 1999<sup>[6]</sup>.

The lower frequency of GERD in Asian populations in the early 90's was unlikely to be solely caused by the known extrinsic risk factors. Genetic factors were probably involved as Asians have a smaller parietal cell mass and a lower acid output compared with Caucasians. The lower prevalence of *hiatus hernia* and smaller body mass index in the Asian population might also have accounted for the lower prevalence of GERD in Asia<sup>[7]</sup>. The cause of the opposing time trend of GERD and duodenal ulcer disease in Asia was unclear but might be related to the declining rate of *Helicobacter pylori* (*H pylori*) infection, or lifestyle changes, such as increased dietary fat intake.

However, similarities exist in Asian and Western patients with GERD. Interestingly, pathogenic factors of reflux esophagitis in Asians were found to include lower esophageal sphincter competence, esophageal peristaltic contractility, and esophageal acid exposure<sup>[8]</sup>, which were identical to results in Western studies. Elderly Chinese patients were found to have more severe gastroesophageal reflux and esophageal lesions compared with their younger counterparts<sup>[9]</sup>.

## GERD AND *HELICOBACTER PYLORI*

Although the relationship between *H pylori*, peptic ulcer disease and gastric malignancy is well established, the link between *H pylori* and GERD remains controversial.

In a systemic review of 20 studies<sup>[10]</sup>, the prevalence of *H pylori* infection in subjects with GERD was significantly lower than that in those without GERD. Geographical location was a strong contributor to the heterogeneity between studies. Although the prevalence of *H pylori* in the general population was found to be higher in the East, patients from the Far East with reflux disease had a lower prevalence of *H pylori* infection than patients from Europe and North America.

Since associations do not prove causality, a more pertinent question is whether eradication of *H pylori* increases the risk of GERD. Hamada and colleagues<sup>[11]</sup> addressed this question by comparing the prevalence of new onset reflux *esophagitis* among 286 patients who underwent *H pylori* eradication therapy with that of 286 age- and disease-matched *H pylori*-positive controls who did not undergo eradication therapy. Within 3 years of follow-up, 18 % of those who had successful eradication of *H pylori* developed reflux *esophagitis* and this prevalence was higher than the 0.3 % recorded among those without therapy. Reflux esophagitis, when present was mild in most cases. The presence of *hiatal hernia* and severe corpus gastritis was closely related to the development of reflux esophagitis after *H pylori* eradication therapy. The data suggested that increased gastric acid secretion after *H pylori* eradication might only be one of the several factors responsible

for the increased risk of GERD following *H pylori* eradication. On the other hand, in a post hoc analysis of 8 prospective double blind US trials of *H pylori* therapy for patients with active duodenal ulcers or a history of duodenal ulcers<sup>[12]</sup>, no difference was found in the likelihood of developing new GERD symptoms or *esophagitis* in individuals cured of *H pylori* infection compared with those with persistent infection. There was no association of *H pylori* eradication with worsening symptoms in those with preexisting GERD. The likelihood for patients who were successfully cured of their *H pylori* disease to experience a worsening of their GERD symptoms was less than that for those with persistent infection (odds ratio: 0.47, 95 % confidence interval: 0.24-0.91). However, this study had its limitations. Although the overall number of subjects included in the analysis was large, the numbers of patients in some of the subgroup analyses were small. In addition, follow-up was less than 2 months in 7 of the 8 studies included in the analysis. Nevertheless, this study suggested that *H pylori* eradication should not be withheld for fear of causing or worsening GERD. The findings in this study that patients with preexisting GERD were less likely to develop worse symptoms must not be taken to mean that patients with GERD improved after *H pylori* eradication. At present, the treatment of *H pylori* in patients with GERD remains controversial.

## TREATMENT OF GERD

In a study investigating the healthcare-seeking behavior of Asian subjects with heartburn, the decision to medicate and to seek medical advice was linked to symptom severity, but not to ethnicity<sup>[13]</sup>.

The mainstay of treatment for GERD is acid suppression. Proton pump inhibitors provide the most rapid symptomatic relief and the highest healing rates for *esophagitis*. Omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole had all been demonstrated to improve GERD symptoms and to heal *esophagitis*. Interestingly, antireflux therapy has been shown to decrease bronchial hyper-responsiveness and improve pulmonary function in asthmatic patients with GERD<sup>[14]</sup>.

For patients with GERD who do not like the idea of taking long-term proton pump inhibitors, Nissen fundoplication, which was modified to the laparoscopic technique in 1991, is an option. However, its association with significant morbidity and its mortality rate of 0.2 % prompted the birth of innovative endoscopic techniques.

The Stretta procedure, which involves radiofrequency induction of localized thermal energy to lower *esophageal sphincter* or *cardia*, has been shown in a multicentre randomized double-blind sham-controlled trial<sup>[15]</sup> to improve heartburn symptom scores and physical quality of life scores. There was no bleeds, perforations or deaths in this study. Another technique, known as the gatekeeper system, has the unique advantage of allowing addition or removal of implants as necessary and was shown to improve symptoms and decrease requirement for anti-reflux medication<sup>[16]</sup>. A third option, transesophageal endoscopic plication, resulted in significant improvement in lower *esophageal sphincter* pressure and post-procedure 24-hour *esophageal pH*<sup>[17]</sup>. Finally, endoscopic implantation of inert materials such as Enteryx has been shown to improve symptom scores, quality of life and 24-hour *esophageal pH*, with reduction in the use of acid suppression 6 months after treatment<sup>[18]</sup>.

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