Reasons for the Rise of Gastroesophageal Reflux Disease in Asia

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Abstract

Gastroesophageal reflux disease (GERD) was considered an uncommon disease in Asia in the past but is now a rapidly emerging disease. Various factors underlie this rise, which can be broadly divided into environmental and host genetic factors. Among these factors, the rapid increase in overweight and obesity in the region is probably the most important. Other factors include lifestyle changes which have accompanied "Westernization" of the Asian population, including a change in diet, smoking, alcohol consumption, and physical activity, but these are often hard to measure. A decline in *Helicobacter pylori* infection across the region likely plays an important role as well. Ethnic differences and differences in the rate of rise of GERD between ethnic groups in the region point to a key role for host genetic factors. Genetic polymorphisms which involve the interleukin-1B gene have been reported, but more work needs to be done in this area.

Keywords

Gastroesophageal reflux disease • Rise in disease prevalence • Asia • Ethnic differences • Obesity • *H. pylori* infection • Lifestyle changes

Introduction

Once considered an uncommon disease among Asians [1], gastroesophageal reflux disease (GERD) has increased dramatically over the past two decades in the Asia-Pacific region. Many reasons underlie this change. A better awareness and recognition of the disease by patients and doctors have led to an increase in the diagnosis of

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the disease, but most experts feel that there is indeed a "real increase" in the disease in this part of the world [2–4]. The reasons for this increase can be broadly divided into extrinsic, or environmental, and host genetic factors.

Environmental Causes

The increase in GERD in Asia has often been attributed to readily identifiable environmental causes, but scientific evidence to support these has often been lacking (Table 3.1).

Change in Diet

Dietary change has been inevitable with growing affluence in many parts of Asia. An increase in the consumption of dietary fat and protein among Asian populations is well documented [5–8]. The role of diet in the causation of GERD has been widely discussed. El-Serag, in a cross-sectional survey, reported an association between high dietary fat and increased risk of reflux disease [9]. Fox et al. showed a high-fat and high-calorie diet increased the severity and frequency of reflux symptoms [10]. In an earlier study from China, Pan et al. showed that eating "greasy and oily" foods is a cause of reflux symptoms [11]. A recent multicenter Indian Society of Gastroenterology Task Force study showed that consumption of nonvegetarian (with a high animal fat content) and fried foods was an independent predictor of GERD [12]. Physiological studies on healthy volunteers and reflux patients have shown an increased transient lower esophageal sphincter relaxation (TLESR) with ingestion of fatty foods [13–15]. It is important to note that dietary fiber, on the contrary, in the El-Serag et al. study, was shown to be protective against reflux disease.

Table 3.1 Causes of increase in GERD in Asia

	Strength of evidence	
Obesity	+++	For both erosive esophagitis and GERD symptoms with an increase in BMI, increase in abdominal girth and visceral adiposity
High-fat diet	+	Limited studies
Smoking	±	
Alcohol intake	+	Limited studies
Ingestion of carbonated drinks	±	No direct evidence
Ingestion of chilies	±	Conflicting data
Physical inactivity	+	No direct evidence
Disappearing *H. pylori* infection	++	
Host genetic factors	++	Different susceptibility of different Asian races

Key: +++ very strong, ++ strong, + modest, ± inconclusive

What about other types of foods? Spicy foods are the normal fare on many Asian tables. Spicy food incorporating chilies have been universally incriminated as a cause of dyspepsia and acid reflux symptoms. But evidence to refute or support this notion is sparse. Capsaicin, which is the active ingredient of chili, has been shown to induce reflux symptoms [16]. In a review of the influence of diet and reflux symptoms in Korea, a wide range of foods including spicy and fatty foods were found to be associated with reflux symptoms, as were carbonated drinks and coffee [17]. Lim et al. showed that curry provokes acid reflux and reflux symptoms [18]. Gonlachanvit reviewed the literature and wrote that although spicy foods aggravated acute abdominal pain and burning symptoms, spicy food and rice in fact improved GERD symptoms in the longer term [19].

Consumption of carbonated drinks has increased exponentially in many parts of Asia with the rapid urbanization and Westernization of the population, and has been postulated as a cause for the increase in GERD in Asia. Carbonated drinks have been shown to increase the number of TLESRs and to lower the esophageal sphincter pressure [20], but this does not seem to translate to an increase in GERD in the real-life situation [21].

Several other "refluxogenic" foods and drinks that lower the esophageal sphincter pressures have been identified, including chocolate, mint sweets, coffee, and tea. Several Asian studies have shown that consumption of coffee and tea was associated with GERD [12, 17]. However, a recent meta-analysis from Korea did not show a correlation between coffee consumption and GERD [22]. Nonetheless, there has been no marked change in coffee or tea consumption in recent years in the Asian population.

Dietary studies remain difficult to perform in terms of accurate measurement of food intake, and results are therefore often difficult to interpret, with low odds ratio and wide confidence intervals.

Cigarette Smoking and Alcohol Consumption

In several epidemiological studies from Asia, smoking has been shown to be a consistent risk factor for reflux disease among Asians. It is estimated that the risk is at least twofold for smoking [23, 24]. Smoking has been shown to be increasing in the Asia-Pacific region [25]. A decrease in lower sphincter pressures that can occur with long-standing smoking is believed to be the putative mechanism [26, 27].

The association between alcohol consumption and GERD has also been reported in several Asian epidemiological studies. Watanabe et al. showed an association for both cigarette smoking and significant alcohol consumption with GERD [28]. Rosaida and Goh showed a strong association of alcohol intake with both reflux esophagitis and nonerosive reflux disease [29]. Alcohol can similarly lower the esophageal sphincter pressure and has also been shown to sensitize the lower esophageal mucosa in accentuating the pain associated with reflux episodes [30–32]. Alcohol intake has also been shown to be on the rise in the Asia-Pacific region and may be contributing to the observed increase in GERD [33].

Physical Activity

Zheng et al. showed that increased physical activity at work was a risk factor for GERD, while recreational physical activity, conversely, was protective against GERD [24]. However, epidemiological studies have shown a long-term protective effect of exercise [23, 24, 34, 35]. Exercise has actually been shown to increase lower esophageal exposure during exercise. A more sedentary lifestyle associated with a recent change in socioeconomic status and urbanization may have resulted in a decrease in physical activity from a previously predominantly "agricultural-based" lifestyle. This could also indicate that other factors associated with modern living, such as obesity, may be putative, and GERD may not be a direct consequence of a change in physical activity.

An Increase in Body Mass Index and Obesity

Perhaps the most important factor in the emergence of GERD in Asia has been the marked increase in the prevalence of obesity and metabolic syndrome in the region [36]. Obesity has indeed become a major problem in Asians. Recent surveys from China have shown that overweight and obesity affects a significant proportion of the population [37–39]. A recent report from India has also reported a marked increase in BMI in their population [40]. Obesity and its attendant associated diseases such as cardiovascular disease, diabetes mellitus, and nonalcoholic fatty liver have been reported to be on the increase in the Asia-Pacific region [41–43].

In a meta-analysis of published studies, Hampel and colleagues have shown that obesity is associated with increased reflux symptoms, erosive esophagitis, and esophageal adenocarcinoma [44]. Many studies from Asia correlating obesity [45, 46] and metabolic syndrome [46–50] with reflux disease have now been published. In particular, the association between visceral adiposity and central obesity has been consistently significant [47, 51–54].

The mechanisms of disease causation—increased intra-abdominal pressure, impaired gastric emptying, decreased lower esophageal sphincter tone, and an increase in the number of transient lower esophageal sphincter relaxations—have been demonstrated in obese subjects [55–59]. A study by Pandolfino et al. employing sophisticated manometric techniques showed an increase in intragastric pressure as well as gastroesophageal pressure gradients in obese individuals [60].

The "epidemic" of obesity in Asia portends a similar exponential increase in obesity-related disease such as GERD.

Disappearing *H. pylori* Infection

An opposing time trend with a decline in *H .pylori* infection and an increase in GERD has been observed throughout the world, including in the Asia-Pacific region [61, 62]. The putative mechanism is inflammation of the gastric mucosa caused by

H. pylori infection, which results in a decrease in acid secretion and a consequent decline in acid-related diseases including GERD and peptic ulcer disease.

Cross-sectional and case-control studies from Asia have shown a consistent inverse relationship between the prevalence of *H. pylori* and GERD [63–66]. Further support for the role of *H. pylori* infection is shown by a stronger negative association with more virulent strains of *H. pylori* (CagA-positive strains) [67, 68].

Reports on the association between *H. pylori* eradication and GERD have, however, been conflicting. Koike et al. showed an increase in gastric acid with *H. pylori* eradication [69]. Wu et al. showed that *H. pylori* eradication led to more "difficult to treat" cases of GERD [70]. Hamada et al. and Inoue et al. have both shown an increase in incidence of erosive esophagitis after *H. pylori* eradication [71, 72]. However, Kim et al. [73] reported no association with *H. pylori* eradication, and Tsukada et al. found an association only in patients with hiatus hernia [74]. In a meta-analysis of seven randomized controlled trials and five cohort studies, no significant difference in the prevalence of erosive or symptomatic GERD was seen in those patients who had *H. pylori* successfully eradicated and those who had a persistent infection [75].

H. pylori especially with the antral predominant or duodenal ulcer phenotype is associated with an increase in gastric acid secretion. This would normalize with *H. pylori* eradication. On the other hand, the corpus predominant or pangastritis phenotype of *H. pylori* infection is associated with a decrease in gastric acid secretion, and a rebound of acid secretion would occur with *H. pylori* eradication unless irreversible atrophic gastritis has already occurred [76]. This difference in the phenotype of *H. pylori* infection is likely to underlie the variable outcome of *H. pylori* eradication that has been reported.

Host Factors

Ethnic Differences: Genetic Predisposition?

The role of host genetic factors in the pathogenesis of GERD is well shown in two important studies where the prevalence of GERD was higher in monozygotic compared to dizygotic twins [77, 78]. Familial clustering of GERD has also been reported [79]. Several genetic mutations influencing host's inflammatory response, DNA repair, mutagenesis, and esophageal sensory function have been described in association with GERD [80].

In Asia different predisposition to GERD among different ethnicity points to a role of host genetic factors and/or environmental factors such as diet common or peculiar to an ethnic group as putative.

High prevalence for GERD symptoms among Chinese, Japanese, and Koreans indicates that these races may be predisposed to develop GERD in the first place. In a multiracial country like Malaysia, with three major Asian races—Malay, Indian, and Chinese—it is possible to compare changes between these races living in the same environment. Rosaida and Goh identified Indian race as a risk factor for GERD

and erosive reflux esophagitis [29]. In another study, Rajendra et al. showed a distinct predisposition to develop Barrett's esophagus in Indian patients and further showed a predominance of HLA B7 subtype among Indians with the disease [81].

Furthermore, genetic predisposition to GERD among different ethnic groups would mean that such an increase would be more prominent among certain racial groups. This has been demonstrated in a time-trend study, where Goh et al. recorded a significantly higher rise in esophagitis over a 10-year interval among Indians (2.4–8.1%) compared to Chinese (1.7–6.4%) and Malays (1.5–3.7%) [62].

In a particular geographical region in Malaysia, environmental influences remain fairly consistent across all races, as much social intermixing (but not intermarriages) in daily life have taken place. The differential increase in the prevalence of GERD between races marks out Indians as a genetically susceptible race to the influence of changing environmental factors in the development of GERD. Interestingly, a study from the UK lends support to this notion by identifying South Asian race (Indian) vs. White Caucasians as a risk factor for GERD [82].

What specific genetic polymorphisms identify predisposition to reflux disease is, however, still not entirely clarified. Reports of interleukin-1B polymorphisms in studies from India, Japan, and Korea have shown a predilection to GERD in subjects with less pro-inflammatory genotypes [83–85]. More substantive work has still to be carried out in this area of research.

Conclusion

The pathogenesis of GERD is a complex interaction between environmental and host factors. The increase in GERD in Asia is the result of several environmental factors, including a marked increase in obesity across the region, and changes in diet and lifestyle of the population interacting with a genetically susceptible population. In a region with a high *H. pylori* prevalence, the declining rates of the infection are likely to also contribute in a significant way to the increased prevalence of GERD in Asia.

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