
Terminology and Cultural Issues in the Diagnosis and Treatment of GERD in Asia

12

Hardik Parikh and Philip Abraham

Introduction

The Asian continent is the most diverse one with regard to ethnic groups, cultures, habits, and environment. Naturally, disease frequency and etiological factors will vary as widely. A condition such as gastroesophageal reflux disease (GERD) is dependent on diet and environment as much as on the individual and so is an archetypal case for study in such a situation.

GERD Prevalence in Asia

Population-based GERD prevalence data from the USA (28.8%) and Europe (23.7%) had showed significantly higher rates as compared to those in Asia [1]. Approximately 2.5–5% of Asians experience weekly heartburn and/or acid regurgitation [2]. There are substantial differences in GERD prevalence among Asian regions, but only East Asia shows rates consistently lower than 10% [3]. The prevalence is highest in West Asia (12.5–27.6%), less so in Central Asia (7.6–19.4%), and lowest in East Asia (2.5–9.4%) [3]. Rates ranging from 12.4% (Taiwan), 17% (Mainland China), to 29.8% (Hong Kong) have also been reported, though [4–9]. Rates reported from the Indian subcontinent (India, Bangladesh, and Pakistan) range from 7.6 to 24% [5, 6, 10]. The Asian Indian race (South Asia) seems to be at higher risk as compared to white Caucasians for developing GERD [11].

H. Parikh
Department of Gastroenterology, KEM Hospital and Seth GS Medical College,
Mumbai 400012, India

P. Abraham (✉)
Division of Gastroenterology, P.D. Hinduja Hospital,
VS Marg, Mahim, Mumbai 400016, India
e-mail: dr_pabraham@hindujahospital.com

Ethnic differences in the prevalence of GERD within a region were studied in Singapore; a higher incidence was noted in Indians in Singapore (7.5%) as compared to Malays (3%) and Chinese (0.8%) [12]. Racial differences were also reported in a multiracial country like Malaysia, where the prevalence of reflux-type symptoms was more common among Indians (7.5%; 95% CI, 4.4–11.7) than Chinese (0.8%; 95% CI, 0.1–3.0) and Malays (3.0%; 95% CI, 1.2–6.1) [12]. Another study of the prevalence of heartburn in a multiracial population, based on a gastrointestinal symptoms questionnaire, showed that the annual prevalence of heartburn was more in Indians (42.4%) as compared to Chinese (29.3%) and Malays (29%). Indians vs. Chinese odds ratio 1.77; 95% CI, 1.26–2.50, $p < 0.001$; Indians vs. Malays OR 1.80; 95% CI, 1.28–2.54, $p < 0.001$ [13]. Similar differences were seen in the GERD complication rates.

The prevalence of heartburn was similar in Malays (mainly Muslims) and Chinese (mainly Buddhist or Christian), despite difference in their alcohol intake. But this study was limited by the inability to access differences in exposure to environmental factors, such as dietary fat consumption and the prevalence of *cagA*-positive *Helicobacter pylori* (*H. pylori*) infection. These differences necessitate further studies to establish a genetic and/or environmental etiology [2].

There seems to be an increase over time: the prevalence rate of reflux esophagitis on endoscopy in East Asia was 3.4–5.0% before 2000 and 4.3–15.7% after 2005 [14]. One time-trend study reported a significant increase in cases of esophagitis over a 10-year period among Indians (2.4–8.1%), Malays (1.5–3.7%), and Chinese (1.7–6.4%) [15]. There does not seem to be significant change in the prevalence of Barrett's esophagus in Asia over time.

In most Asian patients, GERD runs a benign course, with a majority of the patients having nonerosive reflux disease (NERD); progression from NERD to erosive esophagitis and complications is low [16, 17]. Complicated GERD appears to be more frequent in whites (12.3%), while only 2.8 and 4.8% of black and West Asian patients, respectively, had complicated GERD [16]. There was no GERD-related complication in any East Asian patient in one study [18].

Different Prevalence Rates in GERD Symptoms Due to Differences in Terminology?

Several explanations have been proposed for the reported differences in prevalence rates. These include the common suspects such as smaller body mass of Asians, lower basal as well as maximal gastric acid secretion, increased prevalence of *H. pylori* infection, low-fat Asian diet, and probably less use of alcohol and tobacco (the latter is debatable). Less well-recognized factors include the lack of a universal definition of GERD, lack of a word for heartburn in some languages, differences in physician recognition and diagnostic practices (e.g., reluctance to undergo endoscopy), and differences in referral patterns.

In the majority of prevalence studies, the diagnosis is symptom-based, using the presence of cardinal symptoms like heartburn and regurgitation as indicator of reflux disease. (This may also explain the differences in prevalence rates reported

from the same population in different studies.) When heartburn or acid regurgitation dominates the patient's symptoms, they have very high specificity but low sensitivity for GERD [19]. Atypical or associated symptoms include noncardiac chest pain, acidic taste in the mouth, globus sensation, asthma, and bloating.

Heartburn is typically described as a burning sensation in the chest with discomfort, extending from the upper abdomen to the chest and sometimes to the jaw. As the name suggests, this symptom can easily be confused with cardiac chest pain. There is no word for heartburn in some languages spoken in Asia (Malay, Chinese, Korean, Tamil) [20]. One multiethnic study showed that, as compared to 35% of whites and 46% of blacks, only 3% of Asians complained of heartburn, and as compared to 35% of whites and 54% of blacks, only 13% of Asians understood heartburn appropriately [18]. Regurgitation is even more difficult to describe; in India, for example, in the absence of a single word in the multiple of dialects in the country, the physician needs to describe the sequence of events ("can you feel food or water or any content rising up from the abdomen, maybe even into the mouth?") to elicit understanding and response.

Probably because of language issues and perceptions, Asians seem to present more commonly with atypical symptoms as compared to the rest of the world; a distinction may be made in a clinic, but this is not easily possible in a field study. The lack of translated and validated questionnaires for the diagnosis of GERD makes it even more difficult.

Why the Rising Prevalence Rates?

Multiple environmental factors have been incriminated in the growing incidence of GERD in Asia. These include rising socioeconomic standards with consequent Westernization of lifestyle and diet (a predominantly carbohydrate-based diet to one that contains more protein and fat) and increase in BMI, increasing the use of alcohol and tobacco and presumably decreasing *H. pylori* prevalence (with consequent increase in gastric acid secretion). An increase in gastric acid secretion in the Japanese population since 1970 has been reported, unrelated to *H. pylori* infection; this may be secondary to increase in dietary fat intake [21]. Increased awareness of disease and improvement in available diagnostic techniques also could play a role. The contribution from stress in a more competitive society to the initiation or aggravation of symptoms of GERD has not been quantified.

Factors Impacting Pathophysiology

Although there is no strong reason to suspect that there would be differences in the basic pathophysiological factors for GERD between ethnic groups and regions, the fact remains that there are limited studies in this regard. Normal reference values for esophageal pH and manometry among racial groups are presently not available; this may be important considering the lower acid outputs recorded in Asian populations. Chinese patients with GERD who underwent esophageal manometry and 24-h

ambulatory esophageal pH monitoring were no different from control subjects in the frequency of transient lower esophageal sphincter relaxation (TLESR), but had significantly lower successful primary peristalsis (59% vs. 70%, $p = 0.04$), suggesting impaired esophageal clearance by defective peristalsis [22]. Hiatal hernia is an infrequent finding in Asian GERD patients even in the presence of esophagitis [23, 24].

Obesity is an important risk factor for GERD. An independent association between increasing abdominal girth and GERD symptoms was identified in whites but not in blacks and Asians [25]. Another symptom-based study showed consistent association between abdominal girth (independent of BMI) and reflux-type symptoms in the white population but not in the black population or Asians [25]. A recent study found a homogeneous increase in GERD prevalence with increasing BMI in US studies, whereas studies from Europe provided heterogeneous results [26]. BMI cutoff points to define obesity and overweight are lower in Asian countries than those currently used in Western countries, but this may not be applicable to all ethnic groups. For the same body fat, African Americans had lower BMI (1.3 kg/m²) as compared to Chinese (1.9), Thais (2.9), Indonesians (3.2), and Ethiopians (4.6) [27].

Factors Impacting Treatment

The current standard of medical care for the treatment of GERD is proton pump inhibitors (PPI). The principal enzyme involved in PPI metabolism is the cytochrome p450 isoform CYP2C19, the phenotypes of which are classified into extensive, intermediate, and poor metabolizers [28]. Studies on racial differences in CYP2C19 genotype polymorphism had shown a higher frequency of poor metabolizers among Asians (11–24%) as compared to 2–5% among whites [29]. Healing rate of erosive esophagitis was only 77% in extensive metabolizers as compared to 95 and 100% for intermediate and poor metabolizers, respectively ($p < 0.05$) [30]. CYP2C19 genotype was not found to be associated with reflux symptoms or esophageal acid exposure [31]. Although in clinical practice CYP2C19 genotype determination is unlikely to predict efficacy of a PPI, a recent study suggested that lower dose of PPI may be sufficient to control reflux symptoms in Asian populations with their lower acid secretory capacity [32]. In patients with severe esophagitis who are refractory to standard treatment, the possibility of their being extensive metabolizers should be considered.

Cultural Differences in Treatment: The Use of Complementary and Alternative Medicines

Complementary and alternative medicines are those that are not an integral part of conventional allopathic medical practice; their use in the treatment for GERD is probably more frequent in Asian regions where they have existed for centuries for treatment of all kinds of illnesses. One study reported that 6.7% of patients use

alternative treatment for heartburn [13]. These include milk, peppermint, botanicals and mixtures of herbs, melatonin, yoga, acupuncture, magnet therapy, hypnosis, massage, and other relaxation techniques. Some of these are detailed below.

Yoga

Forms of yoga involving breathing control techniques (*pranayama*), like *kapalbhati* and *agnisar kriya*, increase diaphragmatic tone and thereby can decrease gastroesophageal reflux. *Kapalbhati* involves passive inspiration and active expiration using abdominal muscles for clearance of the respiratory passage and strengthening the diaphragm [33]. *Agnisar kriya* is a method in which contracting or flapping of abdominal muscles in and out is believed to help digestion. Apart from increasing diaphragmatic tone, these maneuvers are believed to decrease TLESR and increase lower esophageal sphincter tone [24].

Another possible mechanism by which yoga works is impacting the autonomic nervous system via a relaxation response, which is associated with physiological changes in respiratory rate and lowering of heart rate and blood pressure mediated by reduction in epinephrine [34]. Stress-induced increase in gastric acid secretion may also be decreased in the relaxation phase of yoga [35].

Magnet Therapy

Magnetic bracelets, straps, and blankets, which involve the use of static magnetic fields, are an alternative treatment used for GERD. The LINX system, which is a ring of titanium beads with magnetic cores, connected together with titanium wires, was approved by the US FDA in 2012 for the treatment of refractory GERD [36].

Acupuncture

Acupuncture uses stainless steel needles on specific points along the body (acupoints) to rebalance energy flow; this has been used in traditional Chinese medicine for millennia. Electroacupuncture stimulates needles with an electrical current rather than manual manipulation. Acupuncture possibly works by inhibiting intraesophageal acid and bile reflux [37] as well as increasing LES pressure and reducing TLESR [38]. One study showed that adding acupuncture is more effective than doubling the PPI dose in controlling GERD-related symptoms in patients who failed standard-dose PPI [39].

Botanicals (Herbs)

Lonicera, the Chinese honeysuckle flower, has been evaluated in animal studies as a possible treatment for GERD. In one such study, rats given a preparation of the flower were found to have significant improvement in esophageal lesion scores and thickness of the esophageal mucous membrane [40]. Another product is Iberogast, made with nine herbs, including angelica, caraway, clown's mustard plant, German chamomile, greater celandine, lemon balm, licorice, milk thistle, and peppermint. Trials done earlier for evaluating its efficacy in patients with functional dyspepsia noted symptomatic improvement in the subgroup of patients with GERD-like symptoms [41]. The herbal product spearmint was reported to be useful in the treatment of heartburn, but failed in volunteers [42]. Peppermint oil enhances gastric emptying (especially in the early phase) and, while decreasing pressure in the resting LES, may be beneficial in GERD [42].

Melatonin

Melatonin is produced in the pineal gland, esophagus, and other parts of the GI tract. It has been shown to stimulate LES activity, which prevents acid-pepsin-induced esophagitis; it also protects the gut mucosa from oxidative damage caused by reactive oxygen species [43]. One small study involving 36 patients, to evaluate the role of exogenous melatonin alone or in combination with omeprazole in the treatment of reflux disease, showed that the combination therapy was preferable [44].

Milk

Milk can temporarily buffer stomach acid, although it can also stimulate acid production due to its fat content; its efficacy in the treatment of GERD has not been proven.

Conclusion

The multiethnic, multicultural spectrum of Asia makes it a suitable region for study of the role of these factors and diet on GERD prevalence, pathophysiology, and treatment. Unfortunately, there is a paucity of studies addressing these aspects from many parts of Asia, and available studies are largely from regions that in recent decades have had strong Western influences. Basic pathophysiological factors may be common with the West, but studies show differences in prevalence and intensity and recent time-trends changes. PPI is the standard of care for treatment of GERD in Asia, especially in institutes, but alternative treatment modalities are quite frequently in use.

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