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Gastro-Oesophageal Reflux Disease in Asia

Birth of a 'New' Disease?

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Abstract

Gastro-oesophageal reflux disease (GORD) is one of the most common gastrointestinal diseases in the Western world and imposes a heavy burden on society. Although its prevalence in Asia is much lower, there is evidence that this is rapidly rising in Asia. The reported population prevalence of GORD in Eastern Asia ranges from 2.5% to 6.7% for at least weekly symptoms of heartburn and/or acid regurgitation. In general, Asians tend to have a milder spectrum of the disease. Most Asian patients have non-erosive GORD; erosive oesophagitis is less commonly seen than in the Western population. Complicated GORD, such as oesophageal stricture and Barrett's oesophagus, is seldom encountered. The mechanisms of GORD may be different in the Chinese population compared with the Western population. Chest pain is the most predominant extra-oesophageal manifestation of GORD in China, whereas an association with asthma has been shown in Japanese patients. The prevalence of GORD appears to be increasing and possible factors for GORD in Asian populations include *Helicobacter pylori* infection, obesity and increasing dietary fat intake. The adoption of a Western lifestyle in many developing Asian countries may account for the increasing prevalence of GORD. Proton pump inhibitors remain the most effective medical treatment for GORD. GORD will undoubtedly be a great challenge to clinicians both in primary care and in gastroenterology practice in the Asia-Pacific region in the coming years.

Gastro-oesophageal reflux disease (GORD) is a common disease in the Western world. It has been estimated that between 10% and 30% of the population is affected by GORD.[1] In 2002, GORD was reported to incur the highest annual direct costs in the US and cost more than $US9.3 billion per year.[2] GORD is believed to be less prevalent in Asian countries and the perception is that Asians tend to have a milder spectrum of the disease. This may be partly as a result of under-recognition or it may truly reflect a lower frequency of the disease in this region. However, the prevalence and impact of GORD seem to be increasing.

1. Definition of Gastro-Oesophageal Reflux Disease (GORD)

The study of GORD and its epidemiology has been restricted by the lack of consensus over the definition of the disease. The Genval Workshop defined GORD as an illness due to the reflux of gastric contents into the oesophagus, leading to physical complication or significant impairment in quality of life.[3] The working group of the Asia-Pacific consensus on the management of GORD defined GORD as "a disorder in which gastric contents recurrently reflux into the oesophagus causing heartburn and other symptoms".[4] A recent initia-

Table I. Prevalence of gastro-oesophageal reflux disease (reflux symptoms at least once weekly) in different Asian countries

Study	Country/area	Study year	Sample size	Prevalence (reflux symptoms at least once weekly) [%]
Hu et al.[24]	China/Hong Kong	1996	1649	4.8
Wong et al.[13]	China/Hong Kong	2002	2209	2.5
Wong et al.[16] (follow-up study)	China/Hong Kong	2003	772	2.7
Pan et al.[25]	China/Beijing, Shanghai	1996	4992	HB 3.1
Wang et al.[17]	China/Xian	(Not provided)	2789	HB 1.7 AR 3.5
Chen et al.[26]	China/South China	2003	3514	6.2
Cho et al.[27]	Korea	2000–1	1902	3.5
Watanabe et al.[19]	Japan/Kansai	2001	4095	6.7
Fujiwara et al.[18]	Japan/Kansai	2001	6035	6.6

AR = acid regurgitation; **HB** = heartburn.

tive to develop a global consensus for GORD (Montreal definition) defined GORD as a "condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications".[5] In this consensus, it also recognized that gastro-oesophageal reflux not only causes oesophageal syndromes but can also result in extra-oesophageal manifestations, e.g. reflux cough, reflux laryngitis syndrome and asthma.

2. Symptoms of GORD

Heartburn and acid regurgitation are the most commonly encountered symptoms and thus considered typical for GORD. The problem of defining GORD in Asian populations is complicated by the fact that there is no direct translation of the word 'heartburn' in most Asian languages.[6] It has been shown that the word 'heartburn' was interpreted unreliably by patients.[7-10] Spechler et al.[10] examined patients attending general medical clinics and found that 35% of Whites, 46% of Blacks and 3% of East Asian patients reported that they had heartburn ($p < 0.01$), but the term 'heartburn' was understood only by 35%, 54% and 13% of Whites, Blacks and East Asians, respectively, ($p < 0.01$). It has also been recognized that non-cardiac chest pain,[11-13] globus sensation[13,14] and asthma[15] are not uncommon manifestations of GORD in Asian patients.

3. Prevalence of GORD Symptoms

The reported population prevalence of GORD in Eastern Asia ranges from 2.5% to 6.7% for at least weekly symptoms of heartburn and/or acid regurgitation.[13,16-19] Typical GORD symptoms are consistently less common among the general populations of Asia than those in the West, which have a prevalence of around 20% for weekly reflux symptoms (table I).[1,2,20-23]

3.1 Erosive Oesophagitis in Asia

No reliable data are available on the prevalence of oesophagitis in the general population.[28] In case studies, the prevalence of reflux oesophagitis ranged from 3.4% to 16.3%.[29-31] However, these are likely to overestimate the true prevalence. A large study in Hong Kong in patients undergoing routine or emergency upper endoscopy (n = 16 606) showed that 3.8% of the patients had oesophagitis demonstrated by endoscopy; the majority of these patients (94%) had Los Angeles Classification Grade A or B oesophagitis and only 14 patients (0.08%) had oesophageal stricture.[29] A large Japanese study reported oesophagitis in 16.3% of patients visiting a hospital for routine physical examinations (n = 6010) and 87% had mild oesophagitis.[30] Lee et al.[31] examined 7015 patients going for self-paid check-ups and 3.4% of patients were found to have oesophagitis, of which 98.3% were classified as mild oesophagitis. In summary, the prevalence of reflux oesophagitis appears to be lower in the Asian population than in the West.

3.2 Barrett's Oesophagus in Asia

Barrett's oesophagus is characterized by a columnar epithelium replacing the squamous mucosa that normally lines the distal oesophagus and it is believed to be related to the development of oesophageal adenocarcinoma. The prevalence of Barrett's oesophagus varies between different countries. In a study of a multi-ethnic Malaysian population, long-segment Barrett's oesophagus was reported in 1.6% and short-segment Barrett's oesophagus in 4.6% of those undergoing elective endoscopy for upper abdominal or reflux complaints.[32] Indians (8.2%) had the highest prevalence of Barrett's oesophagus (long and short combined) compared with Chinese (5.7%) or Malays (4.4%).[32] A much lower prevalence was found in Southern Chinese patients undergoing upper endoscopy, of whom 0.06% had Barrett's oesophagus (n = 22 628).[29] More data are required to determine the true prevalence of Barrett's oesophagus in Asians.

3.3 Non-Erosive Reflux Disease in Asia

Non-erosive reflux disease (NERD) is defined by the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy.[5] NERD has been reported in >50% of the population in the primary care setting in the Western world.[33-38] In a prospective study, Rosaida and Goh[39] reported that 65.5% of their patients had NERD. In another study from Hong Kong, it was found that 46.7% (215 of 460) of patients with typical reflux symptoms had no endoscopic evidence of oesophagitis.[40] In a study from Singapore,[41] patients with NERD were significantly younger, more likely to have minor psychiatric morbidity and were less likely to respond to proton pump inhibitors (PPIs) compared with patients with erosive oesophagitis.

4. Mechanisms of Reflux in Asia

Transient relaxation of the lower oesophageal sphincter has been implicated as the main pathophysiological mechanism causing GORD in the Western population.[3,42-44] Prolonged oesophageal acid clearance has been attributed to peristaltic dysfunction in patients with GORD.[45,46] However, in a study in Chinese patients, it was found that the frequency of transient relaxation of the lower oesophageal sphincter was similar between patients with GORD and controls.[47] The frequency of such transient relaxation in patients with GORD in the Chinese population (approximately one per hour)[47] was lower when compared with the Western population, which ranged from three to eight per hour in patients with reflux disease and from two to six per hour in healthy subjects.[44] In this study, primary peristalsis was significantly impaired in patients with GORD in the Chinese population, suggesting that oesophageal motor dysfunction may contribute to the development of GORD in the Chinese population. The mechanisms of GORD may be different in the Chinese population compared with the Western population; however, further study will be required to clarify this interesting finding.

5. Is the Prevalence of GORD Increasing in Asia?

The prevalence of oesophagitis in Asia may be increasing.[28,48] An increase in the prevalence of reflux oesophagitis from 3% in the 1970s to 10–15% in the late 1990s has been suggested by a Japanese comparative endoscopic study.[49] In a 1999 re-survey of a cohort of community residents in Singapore who were interviewed in an earlier study in 1994, Lim et al.[50] reported a >6-fold increase in the reporting of reflux symptoms, from a prevalence of 1.6% to a prevalence of 9.9% (figure 1). In a 1-year follow-up study in Hong Kong, Wong et al.[13,16] reported an increase in the annual, monthly and weekly prevalence of GORD symptoms from 29.8%, 8.9% and 2.5%, to 34.1%, 10.1% and 2.7%,

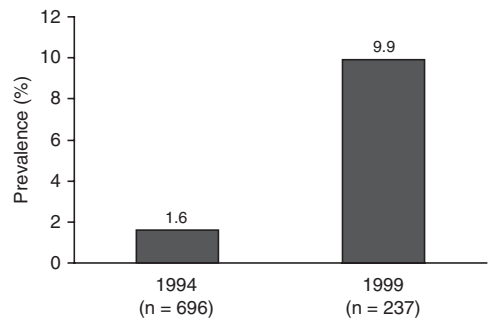

Fig. 1. Increasing population prevalence of gastro-oesophageal reflux disease in Singapore.[50] Increased prevalence was not related to age, smoking, alcohol, bodyweight or ethnicity.

respectively (figure 2). There have been some suggestions that the decrease in *Helicobacter pylori* infections may play a role in the increasing prevalence. The effects of *H. pylori* infection in patients with GORD has been vigorously debated in recent years. Most Asian epidemiological studies reported a lower prevalence of *H. pylori* infection among GORD patients.[51,52] Interventional studies investigating the effect of *H. pylori* eradication on GORD also yielded conflicting results. In a randomized study, *H. pylori* eradication did not produce any effect on symptom relapse after therapy with PPIs.[53] In contrast, another randomized controlled study performed in Hong Kong showed that *H. pylori* eradication led to more resilient GORD that was harder to control.[54] Obesity has been reported to be associated with oesophagitis.[55] An increase in body mass index and moderate weight gain among females of healthy weight has been shown in a recent study that it may cause or exacerbate symptoms of reflux.[56] It has been well documented that a high-fat diet provokes reflux.[57,58] Obesity and increasing dietary fat intake has become more prevalent in the last decade in the Asia-Pacific region with the adoption of a Western lifestyle. These may contribute to the increasing prevalence of GORD in this region.

6. Extra-Oesophageal Manifestations of GORD

A long list of other symptoms in addition to heartburn and acid regurgitation has been demonstrated in subsets of patients with GORD.[59,60] Some of these symptoms originate from the oesophagus and others from the oro-pharynx, larynx and the pulmonary system. In a population study from Hong Kong,[13] a significant association of GORD was found with chest pain, chronic cough and hoarseness of voice, asthma and pneumonia. However, only chest pain remained to be significantly associated with GORD on multiple logistic regression analyses (odds ratio: 2.7; 95% CI 2.1, 3.5). In this study, the prevalence of non-cardiac chest pain was found to be 14%. Being female, reports of symptoms of heartburn and/or acid regurgitation, and feeling that the chest pain compromised social life were independent factors for health seeking behaviour in this Chinese population. The association of GORD and non-cardiac chest pain was supported by a second study from Hong Kong in which abnormal gastro-oesophageal reflux was observed in 29% of chest pain patients with a normal coronary angiogram (n = 78) who underwent 24-hour pH monitoring.[12] An association of GORD with symptoms other than chest pain has been observed with other chronic disorders such as asthma. The treatment of severe reflux oesophagitis has been reported to be associated with the improvement in asthma symptoms in Japan (n = 72).[15] Another study from Japan showed that an improvement in asthma (>20% increase in peak expiratory flow) was observed in 38% of subjects with GORD compared with no improvement in those without GORD.[61]

7. Management of GORD

The main goals in the treatment of GORD are to alleviate symptoms, heal oesophagitis, maintain remission, prevent any complications and improve quality of life.[4]

7.1 Lifestyle Modification

The American College of Gastroenterology updated guidelines for the treatment of GORD[62] state that elevation of the head of the bed, decreased fat, chocolate, alcohol, peppermint and coffee intake, cessation of smoking and avoiding recumbency for 3 hours postprandially may benefit many patients with GORD. However, these recommendations have not been well substantiated. A recent review of the effect of lifestyle measures on GORD[63] showed that there is a lack of high-quality, randomized, controlled studies evaluating lifestyle interventions

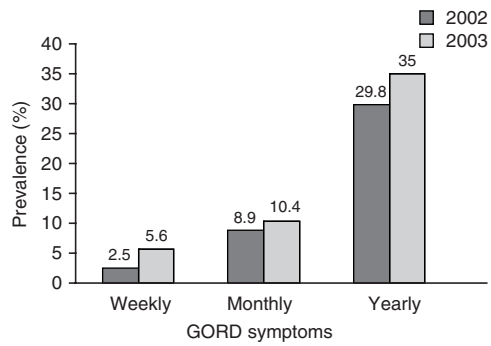

Fig. 2. Increasing population prevalence of gastro-oesophageal reflux (GORD) in Hong Kong over 12 months.[13,16]

in GORD management and there is no convincing evidence for their efficacy. However, lifestyle modifications in the management of GORD should not be discarded entirely because they may play an adjunctive role with acid suppressing therapy or anti-reflux surgery.[64] Future research with well designed, randomized, controlled studies may help to answer this question.

7.2 Medical Treatment

The medications that have been used to alleviate GORD symptoms include antacids, histamine H_2 receptor antagonists, PPIs and prokinetic agents. Antacids have been shown to be more effective than placebo in relieving GORD symptoms;[65] however, the effect of antacids is generally mild. Both H_2 receptor antagonists[66-68] and PPIs[69-72] have been shown to be effective in a large number of studies compared with placebo.[73] However, PPIs are more effective for control of symptoms and healing of oesophagitis than H_2 receptor antagonists.[74-76] Despite this, H_2 receptor antagonists are still used widely in many countries because of their availability and lower cost. Daily PPI therapy results in the healing of about 80% of moderate to severe reflux oesophagitis.[72,77,78] PPIs have been used for more than a decade and have been shown to be well tolerated with minor adverse effects.[79] A lower dose of PPI may be sufficient for control of symptoms in the Chinese compared with the Western population. A study performed in Hong Kong showed that lansoprazole 15 mg once daily provides a satisfactory decrease for oesophageal acid exposure and is equally effective for the treatment of GORD in the Chinese population.[80] Continuous therapy with PPIs has been shown to be effective in the control of symptoms and maintaining remission in patients with oesophagitis.[79] However, it has also been shown that a step-down therapy may be suitable for some patients. A study from the US demonstrated that >50% of the patients can be taken off PPIs and stepped down to H_2 receptor antagonists or even no medication.[81] However, the only advantage of using less-effective therapy is purely economic.[62] As the cost of PPIs decreases, this strategy will become less favourable. Another strategy is intermittent or on-demand therapy. Many patients take their medication intermittently or in an on-demand fashion. Studies have shown that on-demand or intermittent treatments are effective and well tolerated in the management of NERD or mild erosive oesophagitis.[82] The disease spectrum of GORD is milder in Asians and therefore on-demand or intermittent therapy may also be useful for patients in the Asia-Pacific region. However, studies or data focused on patients in this region are lacking and further research in the area will be useful.

7.3 Surgery

Laparoscopic fundoplication is well established as the main surgical treatment of GORD.[83] It corrects the cause of the disease and can prevent the need for long-term medication. One study had shown that during a follow-up period of 10–13 years, patients with complicated GORD who were treated with anti-reflux surgery were significantly less likely to take anti-reflux medications regularly, and when those medicines were discontinued, their GORD symptoms were significantly less severe than those of medically treated patients.[84] However, 62% of surgical patients took medications for GORD on a regular basis, and there were no significant differences between the medical and surgical treatment groups in the rates of neoplastic and peptic complications of GORD, overall physical and mental well-being scores, and satisfaction with anti-reflux therapy.[84] In addition, the benefit of surgery must be balanced against a 0.5–1% risk of operative mortality.[73,85] There are few publications on surgical treatment of GORD in Asia. Studies in Japan have shown that laparoscopic fundoplication can be safe and effective in selected patients.[86,87] Further research from other parts of Asia would be useful.

7.4 Endoscopic Therapy

The Asia-Pacific consensus on the management of GORD concluded in 2004 that endoscopic therapy is still evolving and should be performed in the context of clinical trials.[4] The same statement still holds true today. A lot of enthusiasm was generated when endoscopic treatment of GORD first appeared on the scene. These techniques and devices appeared to produce some improvement in symptoms, although many issues remain unanswered including long-term durability, safety and efficacy in routine

clinical use outside of clinical trials, and its efficacy in atypical presentation of GORD.[62] It is outside the scope of this article to review these techniques in detail; at present, these should only be performed in a clinical trial setting.

8. Conclusions

GORD will undoubtedly be a great challenge to clinicians both in primary care and in gastroenterology practice in the Asia-Pacific region in the coming years. Although typical reflux symptoms are less common than in the Western population, and the prevalence of erosive oesophagitis is lower and of a milder spectrum in the Asian population, the impact of the illness on the general population is huge and there is evidence of an increasing prevalence of GORD in Asia. PPIs remain the most effective medical treatment for GORD. Further research is needed to improve our knowledge of GORD in this region.

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