

Gastroesophageal Reflux Disease in a Low-Income Region in Turkey

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OBJECTIVES: Detailed population-based data regarding the prevalence and symptom profile of gastroesophageal reflux disease (GERD) in underdeveloped and developing Caucasian countries are lacking. The aim of this study was to determine the prevalence and clinical spectrum of GERD in a low-income region in Turkey.

METHODS: We used a previously validated reflux questionnaire, which was translated into Turkish and culturally adapted. The questionnaire was applied to 630 randomly selected participants greater than 20 yr old living in a population of 8,857 adults, with a low mean income of \$75/person/month. The reliability and reproducibility of the questionnaire were calculated using the kappa statistic (test-retest). Endoscopy and/or 24-h intraesophageal pH monitoring were used to ascertain its validity in identifying patients with reflux.

RESULTS: The prevalence of GERD symptoms was 10% for heartburn, 15.6% for regurgitation, and 20% for either symptom experienced at least weekly (95% CI). Heartburn and regurgitation were associated with noncardiac chest pain (37.3%), dysphagia (35.7%), dyspepsia (42.1%), odynophagia (35.7%), globus, hoarseness, cough, hiccup, nausea, vomiting, belching, and NSAID use, but not with body mass index in both frequent and occasional symptom groups. The prevalence of heartburn symptoms, but not regurgitation, increased significantly with age.

CONCLUSIONS: The prevalence of GERD in a low-income population in Turkey was similar to that of developed countries, although with a different symptom profile, namely, a lower incidence of heartburn and a higher incidence of regurgitation and dyspepsia. These findings support the contention that there are a large number of patients worldwide in underdeveloped nations with poorly recognized and largely undertreated GERD.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) has emerged as one of the principal sources of morbidity and impaired quality of life in the Western world (1, 2). In distinct contrast, GERD is commonly considered to be a rare disease with minimal public health impact in underdeveloped or developing nations (3–5). This leads to the belief that GERD prevalence determined in Western countries cannot *a priori* be regarded as representative of the broader pattern of world disease. As a result, the role played by GERD in the spectrum of gastrointestinal disease in these countries is largely unknown. Factors that may have an impact on the prevalence and presentation of such GI pathologies, either separately or together (5), include suboptimal sanitary conditions associated with low income and the resulting prevalence of enteric infections; difficulties accessing health-care facilities; fewer aggregating medicine usage; dietary factors, such as low fat consumption;

high prevalence of *Helicobacter pylori* (*H. Pylori*) infection, especially in Asian countries; genetic factors (low maximal acid output, small parietal cell mass); lower body mass index and obesity; lower consumption of carbonated drinks, alcohol, tea, coffee, or tobacco products.

Given the extraordinarily high impact of GERD on human health and well being, and the high degree of morbidity associated with its complications, there is a compelling need to define reflux prevalence in the non-Western world. In order to address this need, we aimed to determine the prevalence and clinical spectrum of GERD in a low-income population in Turkey. Since the majority of studies addressing the prevalence of GERD have been performed with different methodologies and questionnaires, a comparison of results among studies is difficult. A widely accepted questionnaire, which was validated by researchers at the Mayo Clinic and subsequently used in several studies, might provide an opportunity to compare results among different countries (6–8). In this

study, patients were defined as having GERD if they reported heartburn and/or regurgitation occurring weekly or more often. It is not known whether this arbitrary cut-off is valid for all cultures. We adapted the questionnaire to be applicable to our population, which is distinct in terms of social and economic status.

METHODS

The study was performed in a small, low-income town, Menderes, in Turkey, about 20 kilometers from Izmir, the third largest city in the country. The population of Menderes comprises 8,857 adults, all Caucasian. Since all residents are registered in the government-supported primary health-care system, we used this system to draw a random sample of adults older than 20 yr of age. Assuming a maximum GERD prevalence of 20% in this population, our required sample size was 630 adults (using a 95% CI with worst acceptable SD of $\pm 3\%$). We randomly selected 758 addresses, which was 20% higher than the required number of participants, to account for the ineligibility of potential participants. Potential participants were excluded if they died or moved from the city before the interview, possessed any mental or psychiatric disease, were unable to communicate due to dementia, refused to attend the survey, or had an incorrect address or name within the registration system. Interviewers attempted to find each selected individual by visiting their homes three times, on three nonconsecutive days. If contact was not possible after three attempts, the individual was excluded from the study. The interviewing process was stopped when the sample size of 630 had been reached.

Development of the Questionnaire

The adequacy of an instrument in a given language does not guarantee its reliability and validity in another, even with a good translation in which the translated version is adequate. Cross-language equivalency requires a comprehensive process that involves not only translation but also testing of the psychometric properties of the instrument in alternative languages (9). We used a reflux questionnaire derived from Locke *et al.* (6), previously validated in an English-speaking Western culture, which was translated into Turkish, linguistically validated, and adapted to the cultural profile of Turkey (10). This questionnaire has been used in different studies in different countries, which allowed us to compare the results.

The process of translation included independent translation, back translation, a pilot test using 15 respondents, and a review and approval by the original questionnaire developers. The validity of the instrument is a reflection of the extent that it assesses the qualities it professes to measure, and this was determined by an expert group, which consisted of gastroenterologists and epidemiologists. Feasibility was assessed in terms of the percentage of nonresponse and missing values, difficulty ratings (interviewer and interviewee), and administration time. Test-retest reliability was analyzed

for each respondent using the Cohen's kappa coefficient in a subsample of 25 respondents who repeated the interview 2–3 wk after the first administration. The test-retest reliability of the Turkish version of the questionnaire was good. The median kappa was 0.82. The internal consistency of the questionnaire was also good. Cronbach's alpha values were all higher than 70%; 90.0% for heartburn, 87.1% for acid regurgitation, 86.5% for abdominal pain or dyspepsia, 90.0% for noncardiac chest pain, and 89.4% for dysphagia.

In order to determine the criterion validity of the questionnaire, a sensitivity-specificity analysis was conducted. This validity was determined by comparing screening results using upper gastrointestinal endoscopy or 24-h pH monitoring with clinical findings.

It was presumed, for the sake of this study, that GERD could be determined on the basis of a composite reflux score (Johnson-DeMeester score) of > 14.75 (11), although we also recognize the possibility of underestimating this association by the nondetection of nonacid reflux. As further validation, the revised questionnaire was applied to 45 people who had previously been identified as having, or not having, clinical GERD from the practice of the principal researcher (SB), by conventional symptom criteria. Classification was assigned according to the presence or absence of heartburn, regurgitation, and GERD. Sensitivity of the questionnaire with regard to heartburn was strong, at 94%. For regurgitation, the sensitivity was 84%, and for GERD, it was 81%.

The period used to assess the prevalence of symptoms was the previous 12 months. The questionnaire was administered in face-to-face interviews at each participant's home. Trained interviewers (volunteer medical students) were employed for data collection. Statistical evaluation was performed using the χ^2 and Student's *t*-test (with a 95% CI). The questionnaire contained 72 questions, plus an additional 29 subquestions. Specific questions were added to account for the cultural profile of Turkey, in particular related to the subjects' general lack of awareness of the term "reflux" or "heartburn." Since this symptom does not exist in the language, a detailed description was given, which asked "Have you had any burning feeling or pain in the middle of your chest bone within last year?" While asking questions, the interviewers routinely pointed to the middle of the sternum. Questions were employed that related to the following:

1. Major (heartburn, regurgitation) and related (dysphagia, odynophagia, chest pain) reflux symptoms and the triggering factors of these symptoms.
2. Associated medical conditions.
3. Past medical history: upper (dyspepsia, nausea, vomiting, belching) and lower (abdominal pain or discomfort) gastrointestinal symptoms; respiratory, throat, and cardiac problems (cough, dyspnea, hoarseness, hiccups, globus, asthma); number of physician visits and diagnostic procedures related to upper gastrointestinal symptoms; medication use (NSAIDs, aspirin, and all drugs related to upper gastrointestinal complaints, plus drugs given for other

Table 1. Domains Captured by the Survey

Heartburn: Duration, frequency, severity, nocturnal heartburn, extension to neck, response to antacids
Acid regurgitation: Duration, frequency, severity, nocturnal acid regurgitation, conditions that interrupted daily activities or prompted a visit to the physician.
Number and reason of physician visits, tests done for heartburn and/or acid regurgitation
Chest pain: Duration, frequency, severity. For individual episodes, whether provoked by hot and cold liquids, inspiration, or heavy exertion, whether identified by the physician as cardiac
Dysphagia: Duration, frequency, severity
Odynophagia: To solids, liquids, or both
Other upper gastrointestinal complaints: Abdominal pain, pain more than 6 times/year, severity of pain
Globus sensation
Burping
Nausea, vomiting
Hematemesis
Hiccups
Respiratory symptoms: Cough (frequency, nocturnal)
Medications (duration, dosage): Use of antacids, H ₂ receptor blockers, proton pump inhibitors, other related medications, nonsteroidal antiinflammatory drugs
Hiatal hernia
Disease of esophagus or stomach
Operation of esophagus
Family member with heartburn
Life style and disease activity: Elevate head of bed, use of cigarettes, coffee, tea, or alcohol.

- health problems); pregnancy; current and past smoking history; alcohol, regular coffee, or tea consumption.
- Family history of heartburn or related esophageal diseases.
 - Demographic and socioeconomic factors, including number of households and children, total monthly income, age, weight, height, employment status, level of education, and marital status.

The domains captured by the survey are listed in Table 1.

Each symptom (heartburn, regurgitation, dysphagia, and chest pain) was scored for frequency and severity by the respondent. Symptom frequency was measured on the following five-point scale: less than once a month, once a month, once a week, several times a week, and daily. We defined "frequent symptoms" as the presence of a major symptom (heartburn and/or regurgitation) occurring at least once a week or more often, as described in the original study (1, 6) and by others (7, 8). We added an additional term, "occasional symptoms," which we defined as the presence of an episode of one of the major symptoms less than once a week within the past year. Any respondent who indicated that he/she had frequent heartburn or regurgitation was accepted as having GERD by the previous definition (1). However, the relationships between occasional symptoms and related symptoms were also evaluated.

Symptom severity was assessed on a four-point scale: mild (I do not notice it if I do not think about it), moderate (it dis-

Table 2. Distribution of Respondents According to Age and Gender and the Prevalence of GERD within Age Groups

Age (yr)	Total			Men			Women		
	n	%	GERD* (%)	n	%	GERD* (%)	n	%	GERD* (%)
18-24	62	9.8	1.9	21	7.6	0.6	41	11.6	1.2
25-34	141	22.4	4.3	60	21.7	1.4	81	22.9	2.7
35-44	162	25.7	5.4	68	24.6	1.2	94	26.6	3.8
45-54	117	18.6	4.1	54	19.6	1.2	63	17.8	2.7
55-64	76	12.1	2.2	33	12.0	0.2	43	12.1	1.8
65+	72	11.4	2.1	40	14.5	0.7	32	9.0	1.2

*At least weekly heartburn and/or acid regurgitation within the age group.

turbs me but does not affect my lifestyle), severe (it affects my lifestyle), and very severe (it markedly affects my lifestyle). Some of these results were compared with the published results of Locke *et al.* from data collected on the population of Olmsted County, MN, which employed a similar questionnaire (1). Medical and pharmacy records from a pooling system within the area were reviewed, and diagnoses related to the upper gastrointestinal tract were recorded.

RESULTS

Demographics and Response Rate

The questionnaire was administered to 758 randomly selected adults between November 1998 and December 1999. These individuals were derived from a total population of 8,857 adults, with a response rate of 83.5%, yielding a sample size of 630. The age and sex distribution of these subjects are shown in the Table 2. There was a slight predominance of females, with 56.2% of all participants being women. The mean number of individuals per household was 4.4, and the mean income was \$75/month per participant (minimum wage was \$100/month in the country).

Prevalence of Symptoms

The prevalence of daily symptoms was 3% for heartburn, 3.2% for acid regurgitation, and 4.9% for either symptom. The prevalence of symptoms occurring at least weekly was 10% for heartburn, 15.6% for acid regurgitation, and 20% for either symptom. The latter constituted a working definition of GERD for the purposes of this study. The prevalence of symptoms occurring at least once a year to daily was 15.9% for heartburn, 32.7% for acid regurgitation, and 37.6% for either symptom. Twenty-two percent of respondents reported having both symptoms at least once in the past 12 months.

Age-associated prevalence rates for heartburn and regurgitation for men and women are shown in Figure 1. The prevalence of heartburn, but not regurgitation, increased significantly with age in women. Interestingly, the rate of heartburn or regurgitation seemed to decrease after 45 yr of age only in men. As a result, the prevalence of GERD in men dropped without reaching a significant level (Table 2). Frequent heartburn and regurgitation were both significantly more common in women ($\chi^2 = 8.83$, $p = 0.003$ for heartburn and

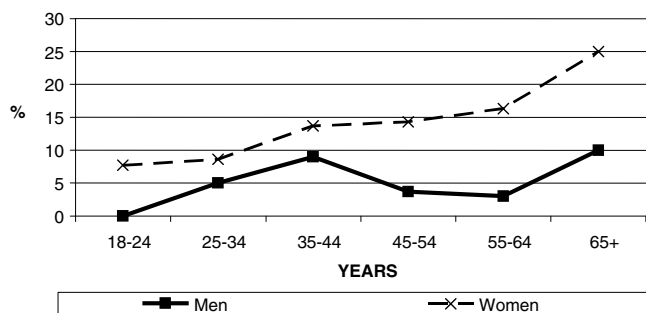


Figure 1. Age- and sex-specific prevalence rates of heartburn in men and women.

$\chi^2 = 20.495$, $p = 0.0001$ for regurgitation). The majority (76.2%) of frequent refluxers were women.

Severity and Duration of Symptoms (Table 2)

Forty-four percent of respondents with heartburn and 28% of respondents with regurgitation reported their symptoms as either severe or very severe. About one-third of respondents who had heartburn and/or regurgitation expressed the duration of their symptoms as being longer than 5 yr (Fig. 2). Married women had a significantly greater risk ($\chi^2 = 19.3$, $df = 2$, $p = 0.0001$ for heartburn and $\chi^2 = 10.9$, $df = 2$, $p = 0.01$ for regurgitation).

Medication Usage

Questions related to medication use for upper gastrointestinal symptoms were posed using generic names first, and classified as antacids and alginates or the pharmacological inhibitors of acid secretion, such as H_2 receptor blockers or proton pump inhibitors. Medication use was higher for individuals with heartburn and regurgitation, and 32.7% of all respondents had used at least one medication related to their upper gastrointestinal problems within the previous year. Respondents with GERD used antacids (34.1%) and acid inhibitors (29.4%) significantly more often than those without GERD symptoms (15.5% for antacids and 10.3% for acid inhibitors, $p < 0.0001$ for both comparisons). Medication

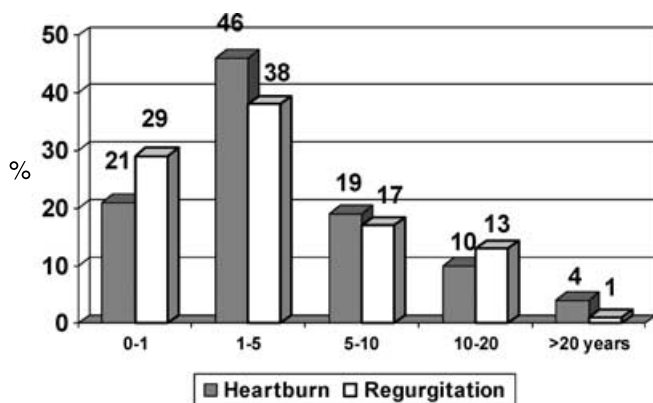


Figure 2. Duration of two major symptoms (%).

was used by 67.7% of respondents with frequent heartburn and 54.1% with frequent regurgitation ($p > 0.05$). Participants with GERD took NSAIDs, but not aspirin, significantly more often (23% vs 12.3%, respectively; $p = 0.002$) than those without GERD. The prevalence of smoking and the consumption of coffee, tea, hot beverages, or alcohol were not significantly different between the group with GERD and those without GERD. Only 14.1% of the study population gave a history of alcohol consumption.

Other Reflux-Related Symptoms

Respondents were divided into three groups according to the frequency of the major symptoms: (i) Frequent symptom group: either of the major symptoms once a week or more often; (ii) Occasional symptom group: either of the major symptoms less than once a week; (iii) No-symptom group: neither of the major symptoms. Additional symptoms, such as noncardiac chest pain, dysphagia, dyspepsia, odynophagia, globus, hoarseness, cough, hiccup, nausea, vomiting, belching, and NSAID use, but not abnormal body mass index, were significantly higher in the frequent symptom group than in the no-symptom group (Table 3). Interestingly, all additional symptoms, except cough and hiccup, were significantly higher in the occasional symptoms group than in the no-symptom group. A third comparison, made between the frequent and occasional symptom groups, revealed that only two of the other symptoms were significantly higher in respondents with frequent symptoms, namely, dysphagia and odynophagia. If the symptom frequency cut-off was on a monthly basis, all mentioned symptoms were still significantly higher in respondents with major symptoms occurring more often than once a month (data not shown). In the context of this study, asthma was recognized as present only if it had been diagnosed by a medical professional and would, therefore, be underestimated if health resources are poor. As such, asthma had been diagnosed in only 1.9% of respondents.

Sociocultural Characteristics of GERD

Review of the pharmacy records prescribed by general practitioners for patients in the target population demonstrated that the term GERD was rarely employed for justification of prescriptions (1.8 GERD diagnoses per 100 patients with upper gastrointestinal symptoms). In order to resolve this difference, we evaluated the extent to which the terms used in conventional history taking were understood by patients. We observed that only 0.2% of those questioned knew the meaning of the term "reflux" or had heard about the disease. In contrast, 50% of those interviewed were familiar with and could explain the meaning of the term "gastritis," which was most commonly applied nonspecifically to the description of all upper gastrointestinal symptoms.

DISCUSSION

Gastroesophageal reflux disease (GERD) is recognized as the most common chronic disease of adults in the United States. A recent U.S. study showed that, among all diseases,

Table 3. Prevalence of Additional Symptoms in Respondents with Major Symptoms (Heartburn and/or Regurgitation)

Symptoms	Olmsted (1) Frequent Symptoms (%)	Menderes					
		Frequent Major Symptoms (N = 126)		Occasional Major Symptoms (N = 111)		No Major Symptoms (N = 393)	
		n	%	n	%	n	%
NCCP	37	47	37.3*	31	27.9*	45	11.5
Dysphagia	29.4	45	35.7* [†]	19	17.1*	21	5.3
Dyspepsia	20.8	53	42.1*	50	45.0*	77	19.6
Odynophagia		45	35.7* [†]	18	16.2*	21	5.3
Globus	14.2	30	23.8*	17	15.3*	24	6.1
Hiccup		12	9.5*	4	3.6	8	2.0
Nausea		76	60.3*	63	56.8*	96	24.4
Emesis		48	38.1*	38	34.2*	64	16.3
Belching		31	24.6*	24	21.6*	45	11.5
Cough		25	19.8*	15	13.5	37	9.4
Dyspnea		61	48.4*	45	40.5*	94	23.9
Hoarseness	23.4	36	28.6*	31	27.9*	35	8.9

* $p < 0.05$ compared with the no-symptom group.

[†] $p < 0.05$ compared with the occasional symptom group.

p -value based on the usual χ^2 test for a 2×2 contingency table.

NCCP = noncardiac chest pain.

GERD was associated with the highest annual direct costs (\$9.3 billion), and that, of these total direct costs, 63% were accounted for by costs of GERD drugs (12). Up to 20% of the population uses over-the-counter antacids or H₂ receptor antagonists for relief of GERD-like symptoms more than twice a week (13). Given the exceedingly large population of the developing world, the impact of GERD and its complications could be highly significant. Yet, studies regarding the prevalence of GERD are localized mainly to westernized countries and are limited by the absence of culture-validated questionnaires and the inadequacies of sample size and response rate (14). We sought to address this problem by administering a culture-specific questionnaire (10) in order to ascertain the prevalence of GERD and GERD complications in an economically depressed region of Turkey. The face-to-face interview technique used in this study yielded a good response rate and was higher than those of studies using phone surveys, such as the AGA-Gallup survey with a 15% response rate (15).

Previous studies of reflux prevalence in developed nations demonstrated that the prevalence of heartburn was 10–48%, the prevalence of regurgitation was 6.5–45%, and the prevalence of either heartburn or regurgitation was 20–59% (16–18). In the DIGEST study, data were collected for a 3-month period from 5,581 people. That study revealed that the prevalence of heartburn and regurgitation were 13.5% and 10.2%, respectively (2). Locke *et al.* performed a study in which a validated questionnaire was administered to 1,511 inhabitants of Olmsted County, MN, by mail (73% response rate) (1). They found that 17.8% of respondents experienced heartburn, 6.3% experienced regurgitation, and 19.8% experienced either symptom at least once weekly. The prevalence of heartburn, but not acid regurgitation, was inversely associated with increasing age. Overall, no significant differences were detected according to age or gender. Symptom severity was reported to be either severe or very severe by 11.3%

of cases, and 60% had a symptom history longer than 5 yr. A recent study from Spain that used the same questionnaire showed a lower prevalence rate—9.8% of respondents had GERD, with a response rate of 71.2% (7).

In contrast, there are few studies of GERD prevalence in the developing world, leading to the misconception that GERD prevalence is low or that it is an insignificant public health risk. The first study of GERD prevalence originating from Asia (Singapore) was performed in 1998 using a validated questionnaire administered by face-to-face interviews to 696 individuals (19). GERD prevalence in that study was decidedly low (1.6%), and the authors of the study hypothesized that this might be related to genetic or environmental factors. However, when the same questionnaire was administered to the same population in the year 2000, 9.9% ($p < 0.05$) now manifested symptoms. Another study was performed in 2,209 people from Hong Kong with a validated Mayo Clinic questionnaire. Monthly and weekly prevalence rates were 8.9% and 2.5%, respectively, showing a low prevalence (8). Additional studies originating from Singapore and China demonstrated that the prevalence of endoscopy-proven esophagitis was between 2–3.3% and 5%, respectively (20, 21), a value that was considerably less than that found in a western counterpart population (10%) (22, 23). The prevalence of GERD might have been climbing rapidly in Asia over the past decade; increasing dietary fat intake, increasing body weight, decreasing *H. pylori* infection rate, and increasing stress levels may all have contributed, but the most important variable is not known.

Currently, there are few GERD prevalence data derived from low-income Caucasian populations in developing or underdeveloped nations. Such regions are remarkable in that they characteristically exhibit high rates of *H. pylori* infection, suboptimal sanitary conditions, and poor access to health-care facilities. Based on the above concerns,

we attempted to evaluate the prevalence of GERD in a representative, low-income, developing nation population in a neighborhood of Izmir, Turkey, called Menderes. We observed that the prevalence of GERD symptoms occurring daily was 3% for heartburn, 3.2% for regurgitation, and 4.9% for either heartburn or regurgitation. The prevalence of GERD symptoms occurring at least weekly was 10% for heartburn, 15.6% for acid regurgitation, and 20% for either symptom. These values for key symptom prevalence were notably similar to previously published GERD prevalence data obtained in Western cultures (1, 2, 7, 15–18). Similarly, the prevalence of extraesophageal symptoms and GERD complications were comparable between Western and non-Western cultures, although with a different symptom profile, namely a lower incidence of heartburn and a higher incidence of regurgitation. Previous studies with this questionnaire defined GERD as the existence of heartburn and/or regurgitation occurring once a week or more often. However, since no differences were found in the additional symptoms (except dysphagia and odynophagia) between the frequent and occasional symptom groups, we assumed that infrequent symptoms should be taken into consideration.

Another interesting point is related to the cultural characteristics of the disease. The terms commonly used in the English language to reflect the presence or absence of GERD, that is, “heartburn” or “reflux,” do not exist in the Turkish language, similar to Chinese or Malay. As such, the majority of patients referred to their upper gastrointestinal symptoms (dyspepsia, heartburn, etc.) simply as “gastritis.” To confirm this, we determined that the diagnosis associated with drug prescriptions for upper gastrointestinal tract symptoms was almost universally “gastritis,” and only a small percentage (1.8%) of patients with upper gastrointestinal tract symptoms were diagnosed as having GERD by primary health-care physicians and internists. This study confirms the high rate of GERD in this population. If the definition of heartburn and regurgitation are distinguished clearly, the actual rate is similar to those reported in developed countries, without considering prescriptions from physicians.

On the other hand, 42.1% of the respondents identified as having GERD in our study by objective criteria (endoscopy, ambulatory pH) actually voiced complaints of dyspepsia. Interestingly, dyspepsia prevalence was found to be approximately 20.8% in a prior prevalence study in a Western culture (1). The prevalence of dyspepsia was 29.3% in a Chinese population from Hong Kong (8). It is conceivable that the high prevalence of dyspepsia in individuals with GERD may, in fact, be related to the relatively high occurrence of *H. pylori* infection. We performed another study in this area and found the incidence of *H. pylori* infection to be 79% using the urea breath test (Bor *et al.*, unpublished data), similar to the rest of the country. It should be emphasized that since *H. pylori* is prevalent in this area, symptoms of peptic ulcer disease, which may mimic those of GERD, may be confounding. We cannot exclude the possibility that *H. pylori* infection provides the context for a different GERD symptom profile.

H. pylori-associated gastritis resulting in acid hyposecretion or modification of the chemical nature of the gastroesophageal refluxate could well contribute to the predisposition to dyspeptic symptoms and the dominant profile of regurgitation as the major symptom present in the country. *H. pylori* infection may also protect against GERD by modifying the acid content of the refluxate (24, 25). Turkey may be of particular interest since it does not appear to possess the predominance of proximal gastric adenocarcinoma that has been so clearly shown in developing countries, possibly related to the higher prevalence of GERD and related complications such as Barrett’s esophagus (26).

We conclude that, once language and cultural factors are considered, the prevalence of GERD and the complications of GERD, are quite similar in Western and non-Western countries. Our findings, if confirmed in larger future population studies, could be highly significant, since they imply the existence of a large population of patients worldwide with poorly recognized or incompletely treated GERD.

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