ORIGINAL ARTICLE

Risk factors and prescription patterns of gastroesophageal reflux disease: HEAL study in Pakistan

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Abstract

Objectives: To determine the frequency of the use of proton-pump inhibitor therapy in patients with typical symptoms of gastroesophageal reflux disease and evaluate its risk factors.

Methods: The cross-sectional study was conducted between June 2010 and February 2011 across 10 cities of Pakistan. Adult patients giving a current history of typical gastroesophageal reflux disease symptoms were included. Information on patient demography, medical history, family history, prescription patterns, lifestyle factors and dietary habits were collected. SPSS 18 was used for statistical analysis and descriptive statistics were used for the analysis of categorical and continuous variables.

Results: Of the 1010 patients enrolled, 954(94.45%) formed the study population. Of them, 520(54.5%) were men. The overall mean age was 41.9±12.5 years, and 439 (46%) had body mass index ≥25kg/m2. Further, 805 (84.4%) reported history of dyspepsia while 692(72.5%) had gastroesophageal reflux disease during the preceding year. Family history of acid peptic disease was reported by 231(24.2%) patients. Prior to consultation, 505(52.9%) patients were on proton-pump inhibitors. Following consultation, 923(96.8%) patients were prescribed proton-pump inhibitors, with omeprazole being the preferred choice in 577(60.5%). Associated risk factors included regular use of nonsteroidal anti-inflammatory drugs in 355(37.2%) and current smoking in 210(22.0%). Consuming spicy meals was reported by 666(70.0%).

Conclusion: Nearly half the patients with typical gastroesophageal reflux disease symptoms were overweight, and a majority consumed spicy meals. Proton-pump inhibitors were widely prescribed, and omeprazole was the preferred choice of drug.

Keywords: GERD, Risk factors, Proton pump inhibitors. (JPMA 64: 751; 2014)

Introduction

Gastroesophageal reflux disease (GERD) is a common affliction and also the major upper gastrointestinal (GI) problem in Western countries with 10-20% of population reporting weekly symptoms of GERD.[1] In Asia, the prevalence of symptom-based GERD during 2005-2010 was 5.2-8.5% in Eastern Asia and 6.3-18.3% in Iran — the country with most studies on GERD prevalence in South Central Asia.[2] Hospital-based studies on GERD from Pakistan have reported a prevalence of 22.2% and 24.0%.[3,4] The total direct and indirect cost of GERD per patient, estimated in purchasing power parity dollars (PPP$) from a study in Iran in 2011, is PPP$97.70 and PPP$13.7, respectively.[5]

GERD influences the general health, daily and social functioning, and physical and emotional activities. It strongly affects the health-related quality of life[6] with frequent interruptions during sleep, work, and social activities. GERD is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[7] Symptoms are considered 'troublesome' if they adversely affect an individual's well-being. The characteristic symptoms of GERD are heartburn and acid regurgitation.[8] Oesophageal and extra-oesophageal symptoms and syndromes like reflux chest pain, sleep disturbances, cough, hoarseness, asthma, and dental erosions form part of GERD symptoms.[7] If untreated, GERD may lead to complications like oesophageal ulceration, stricture, Barrett's oesophagus and development of adenocarcinoma.[8]

Despite the high prevalence of patients suffering with GERD symptoms, the aetiology of the disease is not clearly understood. Environmental and genetic factors[9] are considered as risk factors of GERD. Various lifestyle factors like consumption of alcohol, coffee/tea,[10] soft-drinks, smoking, high body mass index (BMI),[11] usage of non-steroidal anti-inflammatory drugs (NSAIDs),[12] and sleeping position[13] are thought to be associated with GERD. Studies from Pakistan[4] and Korea[10] found that consumption of spicy food was also associated with symptoms in patients with GERD. However, the

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relationship between GERD and these factors has not been firmly established, with inconsistent results from population-based studies.

The treatment strategies for GERD are directed towards acid suppression through lifestyle modifications such as weight loss, elevating the head of the bed, modifying the size and composition of meals, cessation of smoking[14] and use of pharmacologic agents[15] like proton-pump inhibitor (PPI) and histamine 2-receptor antagonist (H2RA) or through surgical treatment. Current guidelines from the American Gastroenterological Association recommend the use of PPIs over H2RAs.[16]

Studies from Pakistan have reported that majority of patients with GERD do not seek healthcare advice, and those who do, consult a physician or general practitioner.[4] However, there is little or no evidence on the risk factors, management and prescription patterns for GERD in patients from Pakistan. This study on risk factors and prescription patterns of gastroesophageal reflux disease (HEAL) was aimed at determining the frequency of use of PPIs in patients with typical GERD symptoms in Pakistan. The secondary objective of the study was to evaluate the risk factors associated with GERD. Further, this study would provide an important perspective on the routine practices in Pakistan and variations from standard treatment guidelines.

Patients and Methods

The national, multi-centre, non-interventional, cross-sectional study was conducted between June 2010 and February 2011 across 10 cities of Pakistan. Based on a recent European study17 and local observations, 80% of patients with symptomatic GERD were assumed to be on empirical PPI therapy. For a 95% Confidence Interval (CI), 2.6% margin of error and a 10% inaccurate completion of data collection forms (DCFs), a sample size of 1000 was determined.

Patients presenting with typical symptoms of GERD, attending primary care centres of various cities in Pakistan over a period of six months were enrolled. Information on patient demography, medical history, family history, prescription patterns, lifestyle factors and dietary habits were collected using a standard DCF.

A total of 99 qualified physicians from 10 cities participated in the study. These were all primary care physicians/general practitioners, who attended to ambulatory patients. Physicians at each centre recruited 10 consecutive patients who met the study criteria. Adult patients presenting with typical symptoms of GERD — heartburn with or without acid regurgitation with the frequency of at least three times a week — and without alarm symptoms like unintentional weight loss, recurrent dysphagia, anaemia, haematemesis and malena, were included in the study. Patients with current or historical evidence of following conditions were excluded: Previous oesophageal, gastric, or duodenal surgery; Zollinger-Ellison syndrome; achalasia; scleroderma and primary oesophageal spasms; oesophageal stricture; upper GI malignancy including dysplastic changes in the oesophagus; active malignant disease; and familial history of oesophageal or gastric cancer. Current or historical evidence included laboratory, endoscopic and radiological findings or past history/diagnosis.

For each patient, information was collected by the physicians on 32 variables.

For primary and secondary analysis all categorical variables were analysed as frequencies and percentages. Continuous variables were reported as means with standard deviations (SD). No comparisons were envisaged as this was a descriptive exploratory study. SPSS 18.0 was used to analyse the data.

The study was conducted at 99 private clinics of general practitioners. Since ethical review committee does not exist for majority of such clinics, administrative approval was taken from each participating clinic/investigator.

The study was conducted according to the guidelines of Good Epidemiology Practice (IEA European Federation, 2004), the principles of the Declaration of Helsinki (1964) and all local laws and regulations. Written informed consent was obtained by the investigators from each patient enrolled in the study.

Results

A total of 1010 patients were enrolled for the study, of which 954 (94.45%) represented the final study sample. Information on 56(5.55%) patients could not be analysed as 3(0.30%) patients did not meet the inclusion criteria, 27(2.67%) met the exclusion criteria, 9(0.91%) had incomplete information, and 17 (1.68%) patients had missing information on primary objective.

Of the final study population, 520 (54.5%) patients were men. The overall mean age of the sample was 41.9±12.5 years and overall mean BMI was 26.9±12.4kg/m^2. There were 439 (46%) overweight patients (BMI $\geq$25 kg/m^2). A family history of acid peptic disease was reported by 231 (24.2%). Further, 805 (84.4%) reported history of

Table-1: Demographic Profile and Medical History of GERD Patients.

Variables (N=954)	n (%)
Gender	
Male	520 (54.51)
Female	434 (45.59)
Age, years*	41.9 (±12.5)
BMI, kg/m^2*	26.9 (±12.4)
BMI ≥25kg/m^2	439 (46.02)
Current symptoms	
Dyspepsia	805 (84.38)
Anxiety	432 (45.28)
Anxiety + restlessness	98 (10.27)
Nightmares	47 (4.93)
Nightmares + restlessness	5 (0.52)
Past medical history	
Dyspepsia during last year	713 (74.74)
History of GERD during last year	692 (72.54)
Headache	426 (44.65)
Family history of acid peptic disease	231 (24.21)
Hyperlipidaemia	132 (13.84)
Smoking history	
Current smoker	210 (22.01)
Past smoker	246 (25.79)
Types of analgesic used	
NSAIDs	355 (37.21)
Aspirin	121 (12.68)
Spicy meals	666 (69.81)
Pickles	478 (50.10)
Raw onions	500 (52.41)

*Values are mean (±SD)
BMI: Body Mass Index
GERD: Gastroesophageal Reflux Disease
NSAIDs: Non-Steroidal Anti-inflammatory Drugs.

dyspepsia while 692(72.5%) had gastroesophageal reflux disease during the preceding year. At the time of consultation, 805(84.4%) patients reported dyspepsia and 432(45.3%) reported anxiety (Table-1).

Besides, 210(22.0%) patients were current smokers, and 246(25.8%) were former smokers; 355(37.2%) were using analgesics like NSAIDs, or aspirin 121(12.7%) regularly. Commonly reported dietary habits included consuming spicy meals by 666(70.0%), pickles 478(50.1%), and raw onions by 500(52.4%). Those taking 3 meals/day numbered 745(78.1%) and 652(68.3%) took 10-20 minutes for consuming each meal. As many as 358(37.5%) patients reported occasionally (<3 times in a month) consuming large volume meals, fast food was reported by 408(43.0%), fried foods 389(41.0%) or soft drinks 269(28.2%). There were 363 (38.05%) patients taking fruits and vegetables 2-3 times/week. While there were 850(89%) patients who had never consumed alcohol, taking tea 1-2 times/day was reported by 556(58.3%) (Table-2).

Overall, 505(52.6%) patients were already using PPIs prior to consultation. At consultation, 923 (96.8%) patients were prescribed PPIs. Omeprazole was the most frequently prescribed medication with a two-fold increase — 289 (30.3%) patients were already taking the drug prior to consultation and 577 (60.5%) patients were prescribed at the time of consultation. There was a decrease in prescription of H2RAs (famotidine, ranitidine and cimetidine) as compared to prior usage. Domperidone was the most frequently prescribed prokinetic agent with an increase in prescription at the time of consultation (n=213, 22.3%) compared to earlier usage (n=87, 9.11%). Among antacid preparations, syrup was being used by 189 (19.81%) patients and was prescribed to 148 (15.51%) patients at the time of consultation (Table-3).

GERD was reported for the first time by 252 (27.0%) patients, with a mean age of 38.8±12.5 years. Mean BMI in this group was 25.9±6.2kg/m^2, and 103 (41.3%) patients

Table-2: Dietary Pattern B of GERD Patients.

Variables	LVM	Fast food	Fried food	Fibres	Coffee	Chocol-ates	Alcohol	Tea	Soft drinks
Never	102 (10.70)	224 (23.48)	95 (10.0)	24 (2.52)	520 (54.51)	501 (52.52)	850 (89.10)	16 (1.70)	48 (5.03)
Occasionally	358! (37.52)	408! (42.77)	389! (40.80)	184! (19.30)	306! (32.08)	324! (34.0)	58! (6.10)	129* (13.25)	532* (55.80)
Once/wk	172 (18.03)	180 (18.87)	177 (18.60)	171 (17.92)	54 (5.66)	47 (4.93)	7 (0.73)	-	-
2-4 times/wk	214 (22.43)	118 (12.37)	211 (22.12)	363 (38.10)	46 (4.82)	36 (3.80)	8 (0.84)	556§ (58.30)	269** (28.20)
> 4 times/wk	98 (10.27)	16 (1.68)	57 (6.0)	184 (19.30)	12 (1.26)	15 (1.60)	8 (0.84)	240$ (25.16)	71+ (7.44)
Missing data	10 (1.05)	6 (0.63)	9 (0.94)	26 (2.73)	15 (1.57)	29 (3.04)	22 (2.31)	11 (1.15)	33 (3.50)

All values are represented as n (%); N=954
βPatients were asked the question: How often do you take? large volume meal ;fast food; fried food; fibres (fruits/vegetables); coffee; chocolate; alcohol; tea and soft drinks.
!(≤3 times/month), *(≤3 times/wk), § (1-3times/day), $ (>3 times/day), **1-2times/day, + > 2 times per/day.
GERD: Gastroesophageal Reflux Disease.
LVM: Large Volume Meal.
wk: Week.

Table-3: Treatment of GERD Patients.

Medications	Past 3 months	Current usage (prior to consultation)	Prescribed today (at consultation)
PPIs			
Omeprazole	340 (35.64)	289 (30.30)	577 (60.50)
Esomeprazole	132 (13.90)	150 (15.72)	231 (24.21)
Lansoprazole	32 (3.40)	26 (2.73)	28 (2.94)
Pantoprazole	22 (2.31)	24 (2.52)	45 (4.72)
Rabeprazole	20 (2.10)	16 (1.70)	42 (4.40)
H2RAs			
Famotidine	126 (13.21)	99 (10.40)	37 (3.90)
Ranitidine	191 (20.02)	118 (12.40)	35 (3.67)
Cimetidine	70 (7.34)	45 (4.72)	5 (0.52)
Prokinetic agents			
Domperidone	125 (13.10)	87 (9.12)	213 (22.33)
Metoclopramide	54 (5.70)	22 (2.30)	36 (3.80)
Cytoprotectives			
Sucralfate	51 (5.35)	28 (2.94)	42 (4.40)
Antacid preparations			
Syrup	294 (30.82)	189 (19.81)	148 (15.51)
Tablet	23 (2.41)	12 (1.30)	7 (0.73)
Compound alginate	19 (2.0)	10 (1.05)	19 (2.0)
Sachet	17 (1.78)	5 (0.52)	5 (0.52)
Others	(3.04)	23 (2.41)	105 (11.01)

All values are represented as n (%); N= 954
GERD: Gastroesophageal Reflux Disease
PPIs: Proton Pump Inhibitors
H2RAs: Histamine 2-Receptor Antagonists.

were overweight. An equal distribution of patients by gender was observed. Family history of acid peptic disease was seen in 26 (10.3%) patients. Among these patients, PPI therapy was prescribed to 244 (96.8%) patients, and for 171 (70.1%) of these patients omeprazole was the preferred choice.

Discussion

The cross-sectional study was conducted to understand the routine practices in the use of PPIs for the management of GERD in Pakistan. To the best of our knowledge, this is the first national study in Pakistan to report the frequency of patients with GERD symptoms receiving PPIs and evaluate the underlying risk factors associated with the disease. It was found that among the 954 eligible patients, 52.97% patients were already on PPI therapy. At consultation, 96.75% patients were prescribed PPIs, with 60.50% patients being prescribed omeprazole. Commonly reported dietary habits included consuming spicy meals (69.81%) and raw onions (52.41%), and many (46.02%) had a high BMI. Smoking and regular use of NSAIDs were also among the prevalent risk factors in this population.

Majority of patients reported typical characteristics of GERD in their medical history. Dyspepsia and a history of GERD symptoms were the major problems reported by patients during the preceding year, and 84.38% patients continued to suffer with dyspepsia even at the time of consultation. In addition, patients experienced psychological feeling of anxiety, restlessness and nightmares or a combination of them. This might be due to the continued psychological distress undergone by the patients. The occurrence of psychological distress with the symptoms of GERD has been observed in a study from Iran[12] where headaches, psychological distress, anxiety, nightmares and restlessness were common in GERD subjects. Family history of acid peptic disease was observed in 231 (24.21%). A previous study in Western population found an association of family history of gastrointestinal disease and GERD symptoms.[18] We hypothesize that this could likely reflect a common sharing of meals that are likely to trigger GERD.

Studies from Western[18] and Asian countries like India[11] and Korea[10] found an association between high BMI and GERD symptoms. Similarly, in this study, 46.02% patients with BMI $\geq$25 presented with GERD symptoms. A previous study from Pakistan suggested that an increasing BMI correlates with greater risk of GERD symptoms.[19] Results from these studies augment the growing body of literature on the association of high BMI with GERD symptoms.

Lifestyle factors such as smoking[18] and use of NSAIDs[20] are known to be associated with GERD symptoms. In this study almost half of the patients with GERD symptoms reported regular usage of either NSAIDs or aspirin. Studies from Iran[12] and Europe[20] reported an association of GERD symptoms in subjects taking NSAIDs or aspirin. Smokers, both current and past, from this study reported GERD symptoms. This is in agreement with studies which reported an association of current smoking and GERD symptoms in Indian[11] (odds ratio = 1.48, 95% CI: 1.19-1.83) and British[18] (odds ratio = 1.65, 95% CI: 1.17-2.33) subjects. Current smoking and use of NSAIDs could therefore be considered as risk factors for GERD in Pakistani population as well.

Dietary and lifestyle modifications are considered the first line of treatment in patients with symptoms of GERD. Consumption of large meals is known to affect the frequency of reflux by increasing gastric distension and transient relaxation of lower oesophageal stricture, and possibly delayed gastric emptying.[21] In

this study, occasional consumption of large volume meals was reported by 37.5% patients. Studies on Indian[22] and Iranian[12] population which have a close cultural similarity to Pakistan, observed an association between GERD symptoms and consumption of fried foods. In this study, 22% of the patients reported consuming fried foods 2-4 times/week. Majority of the patients with GERD symptoms reported dietary habits of 3 meals a day, and 10-20 minutes of meal time. However, an association between the frequency or size of meals and GERD symptoms, to the best of our knowledge, has not been reported by any other studies till date.

Consumption of spicy meals[10] and pickles[12] in the meals are considered as risk factors associated with high prevalence of GERD. Use of pickles and raw onions in meals is routinely followed in Asian countries, especially India, Pakistan, and Iran; while, consumption of spicy meals is followed in most parts of Asia. Observations on the association of consumption of raw onions in meals and GERD symptoms are conflicting. In a study, consumption of onions in meals was found to be refluxogenic in heart burn patients.[23] Whereas observations from India found no association between foods that can precipitate reflux symptoms, such as onions and GERD symptoms.[22] However, in this study, almost half of the patients consumed raw onions (52.41%) and pickles (50.10%) with their meals, while 70% reported consuming spicy meals. Correlation between consumption of pickles and GERD symptoms was observed in Iranian subjects[12] while an association of consumption of spicy food and aggravation of GERD symptoms was observed in subjects from Korea[10] (odds ratio = 1.09, 95% CI, 1.02-1.16) and Pakistan[4] (71% consuming spicy meals).

Existing reports state either no relationship[21,24] or an increased prevalence of GERD symptoms[10] with consumption of alcohol and caffeinated drinks. In this study, majority of the patients presenting with typical GERD symptoms had never consumed alcohol, while about half of the patients had never taken coffee. However, daily intake of tea was reported by 58% patients.

The primary goals of treatment for GERD are relief of symptoms, healing of erosive esophagitis and prevention of complications.[25] About half (52.97%) of the patients in this study reported already using PPIs for treatment of GERD just prior to consultation, while physicians prescribed 96.75% of patients with PPIs at the time of consultation. The practice by physicians in Pakistan is in agreement with the global patterns in pharmacological management of GERD where PPIs are widely used drugs for both short-term and long-term management of GERD.[26] Recent reviews on the treatment of GERD also point that PPIs are the most effective acid suppressants and are the preferred choice of drugs due to their superiority in symptom relief, minimal recurrence of esophagitis and side effects.[25]

The observed increase in prescription pattern of the prokinetic agent, domperidone at the time of consultation (22.33%), compared to earlier usage (9.12%) prior to consultation, might be due to the lesser extrapyramidal effects in patients treated for GERD.[25] However, the decreased prescription pattern of H2RAs might be due to its reduced efficiency in maintenance therapy, prevention of symptom relapse and indicated use in nocturnal symptoms.[25]

The observation of 27.04% of overall patients reporting GERD symptoms for the first time, underlines the poor awareness and recognition of GERD symptoms in the general population. It is essential to understand the epidemiology and risk factors for GERD in a region to design prevention and treatment strategies. The present study had the strength of collecting data on real life clinical practice of physicians in Pakistan. A detailed reporting of various dietary and lifestyle factors of GERD patients was also documented. However, since the study population is limited to specific geographies in Pakistan, the findings need to be cautiously correlated to the entire population of Pakistan.

Conclusion

The majority of GERD patients surveyed were prescribed with PPIs for the management of the disease. Omeprazole was the preferred drug both in patients with a history of symptoms and those reporting symptoms for the first time. Underlying risk factors like consumption of spicy foods, and high BMI were widely prevalent in patients with GERD symptoms.

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